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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 September 2004 (16.09.2004)

PCT

(10) International Publication Number
WO 2004/078770 A1

(51) International Patent Classification[7]: C07H 17/00, 17/08, A61K 31/7048, A61P 31/04, 35/00

(21) International Application Number: PCT/US2004/006892

(22) International Filing Date: 5 March 2004 (05.03.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/451,951 5 March 2003 (05.03.2003) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BIFUNCTIONAL HETEROCYCLIC COMPOUNDS AND METHODS OF MAKING AND USING THE SAME

(57) Abstract: The invention provides a family of bifunctional heterocyclic compounds useful as antiinfective, anti-proliferative, anti-inflammatory, and prokinetic agents. The invention also provides methods of making the bifunctional heterocyclic compounds, and methods of using such compounds as anti-infective, anti-proliferative agents, anti-inflammatory, and/or prokinetic agents.

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BIFUNCTIONAL HETEROCYCLIC COMPOUNDS AND METHODS OF MAKING AND USING THE SAME

RELATED APPLICATIONS

This application claims the benefit of and priority to U.S. Patent Application No. 50/451,951, filed March 5, 2003, the disclosure of which is incorporated by reference herein.

FIELD OF THE INVENTION

The present invention relates generally to the field of anti-infective and anti-proliferative agents. More particularly, the invention relates to a family of bifunctional heterocyclic compounds useful as such agents.

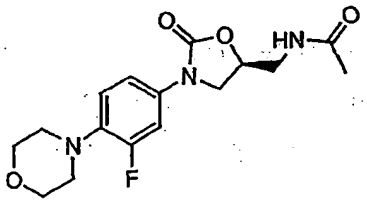
BACKGROUND

Since the discovery of penicillin in the 1920s and streptomycin in the 1940s, many new compounds have been discovered or specifically designed for use as antibiotic agents. It was once believed that infectious diseases could be completely controlled or eradicated with the use of such therapeutic agents. However, such beliefs have been challenged by the fact that strains of microorganisms resistant to currently effective therapeutic agents continue to evolve. Almost every antibiotic agent developed for clinical use has encountered problems with the emergence of resistant bacteria. For example, resistant strains of Gram-positive bacteria such as methicillin-resistant staphylocci, penicillin-resistant streptococci, and vancomycin-resistant enterococci have developed, and can cause serious and often time fatal results for patients infected with such resistant bacteria. Bacteria that are resistant to the macrolide antibiotics have developed. Also, Gram-negative strains of bacteria such as *H. influenzae* and *M. catarrhalis* have been identified. *See, e.g.*, F.D. Lowry, Antimicrobial resistance: the example of *Staphylococcus aureus, J. Clin. Invest.*, Vol. 111, No. 9, pp. 1265-1273 (2003); and Gold, H.S. and Moellering, R.C., Jr., Antimicrobial-drug resistance. *N. Engl. J. Med.*, vol. 335, 1445-53 (1996).

This problem of resistance is not limited to the area of anti-infective agents, because resistance has also been encountered with anti-proliferative agents used in cancer chemotherapy. Therefore, the need exists to develop new anti-infective and anti-proliferative agents that are

both effective against resistant bacteria and strains of cells and against which bacteria and strains of cells are less likely to develop resistance.

Despite this problem of increasing antibiotic resistance, no new major classes of antibiotics have been developed for clinical use since the approval in the United States in 2000 of the oxazolidinone ring-containing antibiotic, N-[[(5S)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl acetamide (see structure **1**), which is known as linezolid and which is sold under the tradename Zyvox® (*see* compound A). *See,* R.C. Moellering, Jr., Linezolid: The First Oxazolidinone Antimicrobial, *Annals of Internal Medicine*, Vol. 138,No. 2, pp. 135-142 (2003).



1

Linezolid was approved for use as an anti-bacterial agent active against Gram-positive organisms. However, linezolid-resistant strains of organisms are already being reported. *See* Tsiodras *et al.*, *Lancet*, 2001, *358*, 207; Gonzales *et al.*, *Lancet*, 2001, *357*, 1179; Zurenko *et al.*, *Proceedings Of The 39th Annual Interscience Conference On Antibacterial Agents And Chemotherapy (ICAAC)*; San Francisco, CA, USA, September 26-29, 1999). However, investigators have been working to develop other effective linezolid derivatives. Research has indicated that the oxazolidinone ring could be important for linezolid's activity. The literature describes molecules having small groups substituted at the C-5 of the oxazolidinone ring, and early structure-activity relationships suggested that compounds with larger groups at the C-5 position were less active as anti-bacterial agents. As a consequence, investigators have been reluctant to place large substituents at the C-5 position of oxazolidinone rings in developing new anti-microbial agents.

Another class of antibiotics is the macrolides, which is so named for the 14- to 16-membered ring that is the major structural characteristic of this class of compounds. The first macrolide antibiotic to be developed was erythromycin, which was isolated from a soil sample from the Philippines in 1952. Even though erythromycin has been one of the most widely prescribed antibiotics, it has the disadvantages of relatively low bioavailability, gastrointestinal side effects, and a limited spectrum of activity. *See* Yong-Ji Wu, Highlights of Semi-synthetic

Developments from Erythromycin A, *Current Pharm. Design* 6, pp. 181-223 (2000), and Yong-Ji Wu and Wei-uo Su, Recent Developments on Ketolides and Macrolides, *Curr. Med. Chem.*, 8(14), pp. 1727-1758 (2001).

In the search for new therapeutic agents, pharmaceutical researchers have tried combining or linking various portions of antibiotic molecules. However, this approach has met with limited success.

U.S. Patent No. 5,693,791, to Truett, issued December 2, 1997 describes an antibiotic of the formula:

A-L-B

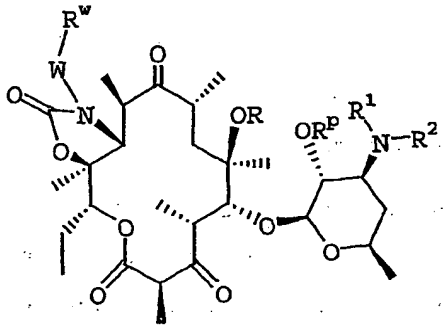
wherein A and B are antibiotics selected from the group consisting of sulfonamides, penicillins, cephalosporins, quinolones, chloramphenicol, erythromycin (i.e., a macrolide antibiotic), metronidzole, tetracyclines, and aminoglycosides. L is a linker formed from a difunctional linking agent.

PCT publication No. WO 99/63937, to Advanced Medicine, Inc., published December 16, 1999, describes multi-binding compounds useful as antibiotics that are of the following formula:

$(L)_p(X)_q$

wherein L is selected from the group consisting of a macrolide antibiotic, an aminoglycoside, lincosamide, oxazolidinone, streptogramin, tetracycline, or another compound that binds to bacterial ribosomal RNA and/or to one or more proteins involved in ribosomal protein synthesis in the bacterium. P is an integer from 2-10. Q is an integer from 1-20. X is a linker.

U.S. Patent No. 6,034,069, to Or et al., issued March 7, 2000 depicts a series of 3'-N-modified 6-O-substituted erythromycin ketolide derivatives such structure 2 below. R, R^1, and R^2 are selected from the group consisting of a variety of groups, including aryl-alkoxy-heteroaryl-alkylene. R^p is H or a hydroxy protecting group. W is absent or is O, NH, or NCH_3. R^w is H or an optionally substituted alkyl group.



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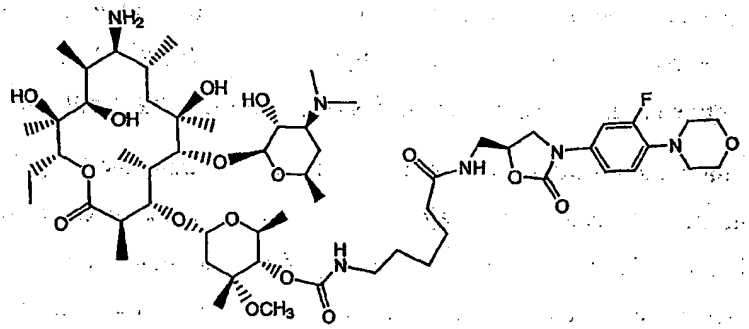
International patent publication No. WO 99/63937 proposes the synthesis of a large variety of multivalent macrolide antibiotics comprising a portion of a macrolide antibiotic linked via a linker to a portion of another known antibacterial agent. Compounds 3 and 4 below are two proposed compounds, although apparently neither was made or tested.



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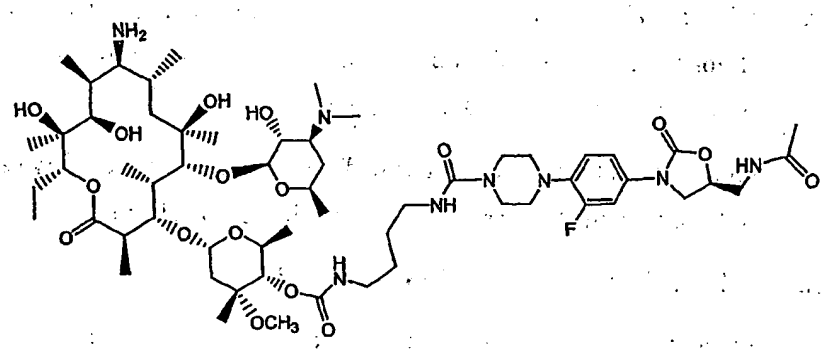

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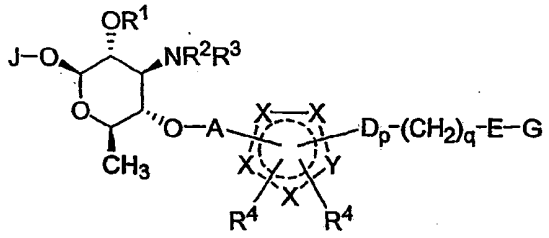
Notwithstanding the foregoing, there is an ongoing need for new anti-infective and anti-proliferative agents. Furthermore, because many anti-infective and anti-proliferative agents have utility as anti-inflammatory agents and also as prokinetic (gastrointestinal modulatory)

agents, there is also an ongoing need for new compounds useful as anti-inflammatory and prokinetic agents.

SUMMARY OF THE INVENTION

The invention provides a family of compounds useful as anti-infective agents and/or anti-proliferative agents, for example, chemotherapeutic agents, anti-fungal agents, anti-bacterial agents, anti-parasitic agents, anti-viral agents, having the formula:



or pharmaceutically acceptable salts, esters, or prodrugs thereof. In the formula, p and q independently are 0 or 1. The variables A, D, E, G, J, R^1, R^2, R^3, R^4, X, and Y can be selected from the respective groups of chemical moieties later defined in the detailed description.

In addition, the invention provides methods of synthesizing the foregoing compounds. Following synthesis, the compounds may be formulated with a pharmaceutically acceptable carrier for administration to a mammal, fish, or fowl for use as an anti-cancer, anti-fungal, anti-bacterial, anti-parasitic, or anti-viral agent. In one embodiment, the compounds or the formulations may be used to treat microbial infections, for example, anti-bacterial or anti-fungal infections, in the mammal, fish, or fowl. Accordingly, the compounds or the formulations may be administered, for example, via oral, parenteral or topical routes, to provide an effective amount of the compound to the mammal, fish, or fowl.

The foregoing and other aspects and embodiments of the invention may be more fully understood by reference to the following detailed description and claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a family of compounds that can be used as anti-proliferative agents and/or anti-infective agents. The compounds may be used without limitation, for example, as anti-cancer agents, anti-bacterial agents, anti-fungal agents, anti-parasitic agents and/or anti-viral agents.

1. Definitions

For the purpose of the present invention, the following definitions have been used throughout.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (e.g., C=C, C=N, or N=N).

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

When any variable (e.g., R^3) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with one or more R^3 moieties, then the group may optionally be substituted with one, two, three ,four, five, or more R^3 moieties, and R^3 at each occurrence is selected independently from the definition of R^3. Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

In the formulas herein, a broken or dashed circle within a ring indicates that the ring is either aromatic or non-aromatic. A bond extending from a chemical moiety that is depicted as crossing a bond in a ring, but is not attached directly to a ring atom, indicates that the chemical moiety may be bonded to any atom of the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. As to any of the above chemical moieties that contain one or more substituents, it is understood that such moieties do not contain any substitution or substitution patterns that are sterically impractical and/or synthetically unfeasible. In addition, the compounds of this invention include all stereochemical isomers arising from the substitution of these moieties.

As used herein, the terms used to describe various carbon-containing moieties, including, for example, "alkyl," "alkenyl," "alkynyl," "carbocycle," and any variations thereof, are

intended to include univalent, bivalent, or multivalent species. For example, "C_{1-6} alkyl-R^3" is intended to represent a univalent C_{1-6} alkyl group substituted with a R^3 group, and "O-C_{1-6} alkyl-R^3" is intended to represent a bivalent C_{1-6} alkyl group, i.e., an "alkylene" group, substituted with an oxygen atom and a R^3 group.

In cases wherein there are nitrogens in the compounds of the present invention, these can be converted to N-oxides by treatment with an oxidizing agent (e.g., MCPBA and/or hydrogen peroxides) to afford other compounds of the present invention. Thus, all shown and claimed nitrogens are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. C_{1-6} alkyl is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkyl groups. C_{1-8} alkyl is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, and C_8 alkyl groups. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl, n-hexyl, n-heptyl, and n-octyl.

As used herein, "alkenyl" is intended to include hydrocarbon chains of either straight or branched configuration and one or more unsaturated carbon-carbon bonds that may occur in any stable point along the chain, such as ethenyl and propenyl. C_{2-6} alkenyl is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. C_{2-8} alkenyl is intended to include C_2, C_3, C_4, C_5, C_6, C_7, and C_8 alkenyl groups.

As used herein, "alkynyl" is intended to include hydrocarbon chains of either straight or branched configuration and one or more triple carbon-carbon bonds that may occur in any stable point along the chain, such as ethynyl and propynyl. C_{2-6} alkynyl is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups. C_{2-8} alkynyl is intended to include C_2, C_3, C_4, C_5, C_6, C_7, and C_8 alkynyl groups.

As used herein, "acyl" is intended to include hydrocarbon chains of either straight or branched configuration and one keto group (=O) that may occur in any stable point along the chain. "C_{1-8} acyl" is intended to include C_2, C_3, C_4, C_5, C_6, C_7, and C_8 acyl groups.

As used herein, "alkoxy" refers to an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. C_{1-6} alkoxy, is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkoxy groups. C_{1-8} alkoxy, is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, and C_8 alkoxy groups. Examples of alkoxy include, but are not limited to, methoxy,

ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, s-pentoxy, n-heptoxy, and n-octoxy.

As used herein, "alkylthio" refers to an alkyl group as defined above with the indicated number of carbon atoms attached through an sulfur bridge. C_{1-6} alkylthio, is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkylthio groups. C_{1-8} alkylthio, is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, and C_8 alkylthio groups.

As used herein, "carbocycle" or "carbocyclic ring" is intended to mean, unless otherwise specified, any stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, or 12-membered bicyclic or tricyclic ring, any of which may be saturated, unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl. As shown above, bridged rings are also included in the definition of carbocycle (e.g., [2.2.2]bicyclooctane). A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge. Fused (e.g., naphthyl and tetrahydronaphthyl) and spiro rings are also included.

As used herein, "halo" or "halogen" refers to fluoro, chloro, bromo, and iodo. "Counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

As used herein, the term "heterocycle" means, unless otherwise stated, a stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, or 12-membered bicyclic or tricyclic heterocyclic ring which is saturated, unsaturated, or aromatic, and consists of carbon atoms and one or more ring heteroatoms, e.g., 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen, and sulfur, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a second ring (e.g., a benzene ring). The nitrogen and sulfur heteroatoms may optionally be oxidized (i.e., $N \rightarrow O$ and $S(O)_p$, where $p = 1$ or 2). When a nitrogen atom is included in the ring it is either N or NH, depending on whether or not it is attached to a double bond in the ring (i.e., a hydrogen is present if needed to maintain the tri-valency of the nitrogen atom). The nitrogen atom may be

substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, as defined). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more atoms (i.e., C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Preferred bridges include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon-nitrogen group. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge. Spiro and fused rings are also included.

As used herein, the term "heteroaryl" or "aromatic heterocycle" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, or 12-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and one or more heteroatoms, e.g., 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen, and sulfur. In the case of bicyclic heterocyclic aromatic rings, only one of the two rings needs to be aromatic (e.g., 2,3-dihydroindole), though both may be (e.g., quinoline). The second ring can also be fused or bridged as defined above for heterocycles. The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, as defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (i.e., N→O and $S(O)_p$, where p = 1 or 2). It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, dihydrooxazole, dithiazolonyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isopyrrolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl,

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oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-oxathiazolyl-1-oxide, oxathiolyl, oxazolidinyl, oxazolyl, oxindolyl, oxo-imidazolyl, oxo-thiazolinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiatriazolyl, thiazoledionyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

The term "hydroxy protecting group" refers to a selectively removable group which is known in the art to protect a hydroxyl group against undesirable reaction during synthetic procedures. The use of hydroxy-protecting groups is well known in the art and many such protecting groups are known (see, for example, T.H. Greene and P.G.M. Wuts (1999) PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, 3rd edition, John Wiley & Sons, New York). Examples of hydroxy protecting groups include, but are not limited to, acetate, methoxymethyl ether, methylthiomethyl, *tert*-butyldimethylsilyl, and *tert*-butyldiphenylsilyl.

The term "macrolide" refers to any compound possessing a 14- or 15-membered macrocyclic ring and derivatives thereof (such as keto, oxime, cyclic carbonate derivatives). These include, for example, compounds that are (or are synthetically derived from) known antibacterial agents including, but not limited to, erythromycin, clarithromycin, azithromycin, telithromycin, roxithromycin, pikromycin, flurithromycin, and dirithromycin.

As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic

acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodide, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicyclic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, and toluene sulfonic.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, **1990**, 1445.

The term "pharmaceutically acceptable ester" refers to esters that hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Other suitable ester groups include, for example, those derived from pharmaceutically acceptable alcohols, such as straight-chain or branched aliphatic alcohols, benzylic alcohols, and amino-alcohols. Examples of particular esters include formates, acetates, propionates, butyrates, acrylates, ethylsuccinates, and methyl, ethyl, propyl, benzyl, and 2-aminoethyl alcohol esters.

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing

the same. "Prodrugs" are intended to include any covalently bonded carriers that release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. It is preferred that the presently recited compounds do not contain a N-halo, $S(O)_2H$, or S(O)H group.

As used herein, "treating" or "treatment" means the treatment of a disease-state in a mammal fish, or fowl, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal fish, or fowl, in particular, when such mammal fish, or fowl is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting its development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

As used herein, "mammal" refers to human and non-human patients.

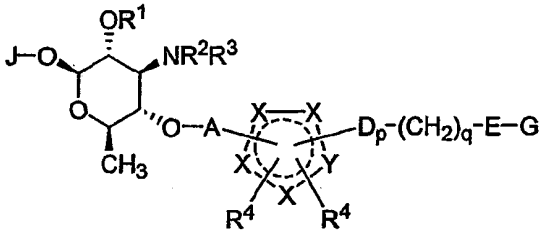
As used herein, the term "therapeutically effective amount" refers to an amount of a compound, or a combination of compounds, of the present invention effective when administered alone or in combination as an anti-proliferative and/or anti-infective agent. The combination of compounds is preferably a synergistic combination. Synergy, as described, for example, by Chou and Talalay, *Adv. Enzyme Regul.* **1984**, *22*:27-55, occurs when the effect of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at sub-optimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased anti-proliferative and/or anti-infective effect, or some other beneficial effect of the combination compared with the individual components.

All percentages and ratios used herein, unless otherwise indicated, are by weight.

Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes are described as having, including, or comprising specific process steps, it is contemplated that compositions of the present invention also consist essentially of, or consist of, the recited components, and that the processes of the present invention also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions are immaterial so long as the invention remains operable. Moreover, two or more steps or actions may be conducted simultaneously.

2. Compounds of the Invention

The invention provides a compound having the formula:

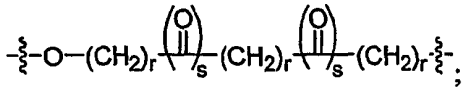


or a pharmaceutically acceptable salt, ester, or prodrug thereof,

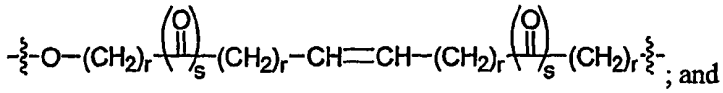
wherein:

-O-A is selected from the group consisting of:

a)

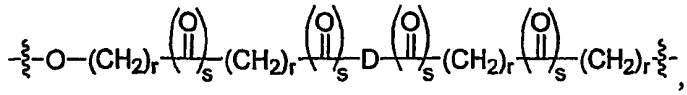


b)



; and

c)



wherein

r, at each occurrence, independently is 0, 1, 2 3, or 4, and

s, at each occurrence, independently is 0 or 1;

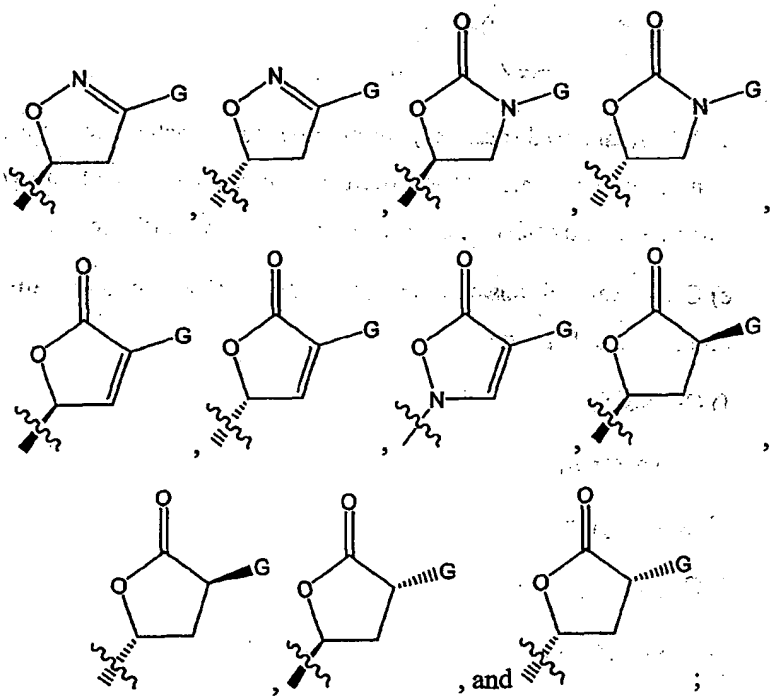
X, at each occurrence, independently is carbon, carbonyl, or nitrogen, provided at least one X is carbon;

Y is carbon, nitrogen, oxygen, or sulfur;

D is selected from the group consisting of:

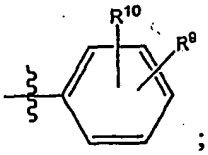
O, S, NR^5, C=O, C=S, C=NOR^5, SO, and SO_2;

E-G is selected from the group consisting of



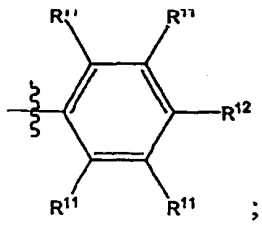
G is selected from the group consisting of:

a)



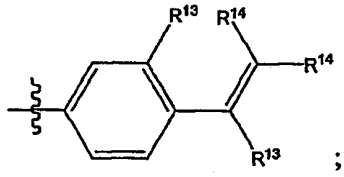
;

b)



;

c)



;

d) 3-14 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and optionally substituted with one or more R^4 groups;

e) C_{3-14} saturated, unsaturated, or aromatic carbocycle, optionally substituted with one or more R^4 groups;

f) C_{1-8} alkyl,

g) C_{2-8} alkenyl,

h) C_{2-8} alkynyl,

i) C_{1-8} alkoxy,

j) C_{1-8} alkylthio,

k) C_{1-8} acyl,

l) $S(O)_tR^5$; and

m) hydrogen,

wherein any of f) – k) optionally is substituted with

i) one or more R^4 groups;

ii) 3-14 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and optionally substituted with one or more R^4 groups; or

iii) C_{3-14} saturated, unsaturated, or aromatic carbocycle, optionally substituted with one or more R^4 groups;

J is selected from the group consisting of:

a) H, b) L_u-C_{1-6} alkyl, c) L_u-C_{2-6} alkenyl, d) L_u-C_{2-6} alkynyl, e) L_u-C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) L_u-(3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), and g) macrolide,

wherein

L is selected from the group consisting of -C(O)-, -C(O)O-, and $-C(O)NR^5-$,

u is 0 or 1, and

any of b) – f) optionally is substituted with one or more R^4 groups;

R^1, R^2, and R^3 are independently selected from the group consisting of:

a) H, b) L_u-C_{1-6} alkyl, c) L_u-C_{2-6} alkenyl, d) L_u-C_{2-6} alkynyl, e) L_u-C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) L_u-(3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), g) L_u-(saturated, unsaturated, or aromatic 10-membered bicyclic ring system optionally containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), and h) L_u-(saturated, unsaturated, or aromatic 13-membered tricyclic ring system optionally containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur),

wherein

L is selected from the group consisting of -C(O)-, -C(O)O-, and $-C(O)NR^7-$,

u is 0 or 1, and

any of b) – h) optionally is substituted with one or more R^4 groups;

alternatively, R^4, and R^5, taken together with the nitrogen atom to which they are bonded, form a 5-7 membered saturated, unsaturated, or aromatic heterocycle optionally containing one or more additional atoms selected from the group consisting of nitrogen, oxygen, and sulfur, and optionally substituted with one or more R^4 groups;

R^4, at each occurrence, independently is selected from the group consisting of:

a) F, b) Cl, c) Br, d) I, e) =O, f) =S, g) $=NR^5$, h) $=NOR^5$, i) $=NS(O)_tR^5$, j) $=N\text{-}NR^5R^5$, k) $-CF_3$, l) $-OR^5$, m) -CN, n) $-NO_2$, o) $-NR^5R^5$, p) $-NR^5OR^5$, q) $-C(O)R^5$, r) $-C(O)OR^5$, s) $-OC(O)R^5$, t) $-C(O)NR^5R^5$, u) $-NR^5C(O)R^5$, v) $-OC(O)NR^5R^5$, w) $-NR^5C(O)OR^5$, x) $-NR^5C(O)NR^5R^5$, y) $-C(S)R^5$, z) $-C(S)OR^5$, aa) $-OC(S)R^5$, bb) $-C(S)NR^5R^5$, cc) $-NR^5C(S)R^5$, dd) $-OC(S)NR^5R^5$, ee) $-NR^5C(S)OR^5$, ff) $-NR^5C(S)NR^5R^5$, gg) $-C(=NR^5)R^5$; hh) $-C(=NR^5)OR^5$, ii) $-OC(=NR^5)R^5$, jj) $-C(=NR^5)NR^5R^5$, kk) $-NR^5C(=NR^5)R^5$, ll) $-OC(=NR^5)NR^5R^5$, mm) $-NR^5C(=NR^5)OR^5$, nn) $-NR^5C(=NR^5)NR^5R^5$, oo) $-NR^5C(=NR^5)NR^5R^5$, pp) $-S(O)_tR^5$, qq) $-SO_2NR^5R^5$, rr) $-S(O)_tN=R^5$, and ss) R^5;

R^5, at each occurrence, independently is selected from the group consisting of:

a) H, b) L_u-C_{1-6} alkyl, c) L_u-C_{2-6} alkenyl, d) L_u-C_{2-6} alkynyl, e) L_u-C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) L_u-(3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), g) L_u-(saturated, unsaturated, or aromatic 10-membered bicyclic ring system optionally containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), and h) L_u-(saturated, unsaturated, or aromatic 13-membered tricyclic ring system optionally containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur),

wherein

L is selected from the group consisting of -C(O)-, -C(O)O-, and $-C(O)NR^8$-,

u is 0 or 1, and

any of b) – h) optionally is substituted with one or more R^6 groups;

alternatively, two R^2 groups, taken together with the atom or atoms to which they are bonded, form i) a 5-7 membered saturated, unsaturated, or aromatic carbocycle, or ii) a 5-7 membered saturated, unsaturated, or aromatic heterocycle containing one or more atoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein i) - ii) optionally is substituted with one or more R^6 groups;

R^6, at each occurrence, independently is selected from the group consisting of:

a) F, b) Cl, c) Br, d) I, e) =O, f) =S, g) $=NR^7$, h) $=NOR^7$, i) $=NS(O)_tR^7$, j) $=N\text{-}NR^7R^7$, k) $-CF_3$, l) $-OR^7$, m) -CN, n) $-NO_2$, o) $-NR^7R^7$, p) $-NR^7OR^7$, q) $-C(O)R^7$, r) $-C(O)OR^7$, s) $-OC(O)R^7$, t) $-C(O)NR^7R^7$, u) $-NR^7C(O)R^7$, v) $-OC(O)NR^7R^7$, w) $-NR^7C(O)OR^7$, x) $-NR^7C(O)NR^7R^7$, y) $-C(S)R^7$, z) $-C(S)OR^7$, aa) $-OC(S)R^7$, bb) $-C(S)NR^7R^7$, cc) $-NR^7C(S)R^7$, dd) $-OC(S)NR^7R^7$, ee) $-NR^7C(S)OR^7$, ff) $-NR^7C(S)NR^7R^7$, gg) $-C(=NR^7)R^7$; hh) $-C(=NR^7)OR^7$, ii) $-OC(=NR^7)R^7$, jj) $-C(=NR^7)NR^7R^7$, kk) $-NR^7C(=NR^7)R^7$, ll) $-OC(=NR^7)NR^7R^7$, mm) $-NR^7C(=NR^7)OR^7$, nn) $-NR^7C(=NR^7)NR^7R^7$, oo) $-NR^7C(=NR^7)NR^7R^7$, pp) $-S(O)_tR^7$, qq) $-SO_2NR^7R^7$, rr) $-S(O)_tN=R^7$, and ss) R^7;

R^7, at each occurrence, independently is selected from the group consisting of:

a) H, b) L_u-C_{1-6} alkyl, c) L_u-C_{2-6} alkenyl, d) L_u-C_{2-6} alkynyl, e) L_u-C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) L_u-(3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), g) L_u-(saturated, unsaturated, or aromatic 10-membered bicyclic ring system optionally containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), and h) L_u-(saturated, unsaturated, or aromatic 13-membered tricyclic ring system optionally containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur),

wherein

L is selected from the group consisting of C(O), C(O)O, and $C(O)NR^7$,

u is 0 or 1, and

any of b) – h) optionally is substituted with one or more moieties selected from the group consisting of:

R^8, F, Cl, Br, I, $-CF_3$, $-OR^8$, $-SR^8$, -CN, $-NO_2$, $-NR^8R^8$, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-C(O)NR^8R^8$, $-NR^8C(O)R^8$, $-OC(O)NR^8R^8$, $-NR^8C(O)OR^8$, $-NR^8C(O)NR^8R^8$, $-C(S)R^8$, $-C(S)OR^8$, $-OC(S)R^8$, $-C(S)NR^8R^8$, $-NR^8C(S)R^8$, $-OC(S)NR^8R^8$, $-NR^8C(S)OR^8$, $-NR^8C(S)NR^8R^8$, $-NR^8C(NR^8)NR^8R^8$, $-SO_2NR^8R^8$, and $-S(O)_tR^8$;

alternatively, two R^7 groups, taken together with the atom or atoms to which they are bonded, form i) a 5-7 membered saturated, unsaturated, or aromatic carbocycle, or ii) a 5-7 membered saturated, unsaturated, or aromatic heterocycle containing one or more atoms selected from the group consisting of nitrogen, oxygen, and sulfur;

R^8, at each occurrence, independently is selected from the group consisting of:

a) H, b) L_u-C_{1-6} alkyl, c) L_u-C_{2-6} alkenyl, d) L_u-C_{2-6} alkynyl, e) L_u-C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) L_u-(3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), g) L_u-(saturated, unsaturated, or aromatic 10-membered bicyclic ring system optionally containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), and h) L_u-(saturated, unsaturated, or aromatic 13-membered tricyclic ring system optionally containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur),

wherein

L is selected from the group consisting of -C(O)-, -C(O)O-, and -C(O)NH-, -C(O)N(C_{1-6} alkyl)-and

u is 0 or 1;

R^9 is R^4;

R^{10} is R^4;

alternatively, R^9 and R^{10}, taken together with the atoms to which they are bonded, form i) a 5-7 membered saturated, unsaturated, or aromatic carbocycle, or ii) a 5-7 membered

saturated, unsaturated, or aromatic heterocycle containing one or more atoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein i) - ii) optionally is substituted with one or more R^4 groups;

R^{11} is R^4;

alternatively, two R^{11} groups, taken together with the atoms to which they are bonded, form i) a 5-7 membered saturated, unsaturated, or aromatic carbocycle, or ii) a 5-7 membered saturated, unsaturated, or aromatic heterocycle containing one or more atoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein i) - ii) optionally is substituted with one or more R^4 groups;

R^{12} is R^5;

alternatively, R^{12} and one R^{11} group, taken together with the atoms to which they are bonded, form i) a 5-7 membered saturated, unsaturated, or aromatic carbocycle, or ii) a 5-7 membered saturated, unsaturated, or aromatic heterocycle containing one or more atoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein i) - ii) optionally is substituted with one or more R^4 groups;

R^{13} is R^4;

R^{14} is R^4;

alternatively, any R^{13} and any R^{14}, taken together with the atoms to which they are bonded, form i) a 5-7 membered saturated, unsaturated, or aromatic carbocycle, or ii) a 5-7 membered saturated, unsaturated, or aromatic heterocycle containing one or more atoms selected from the group consisting of nitrogen, oxygen, and sulfur,

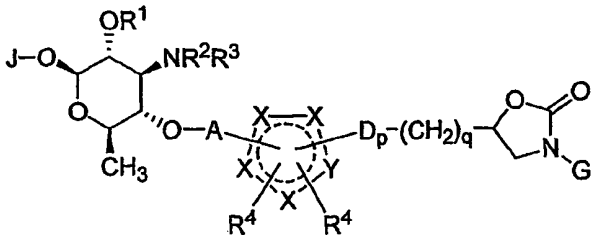
wherein i) - ii) optionally is substituted with one or more R^4 groups;

p is 0 or 1;

q is 0 or 1; and

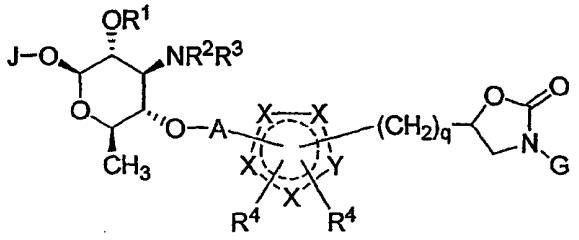
t, at each occurrence, independently is 0, 1, or 2.

In certain embodiments, the invention provides compounds having the formula:



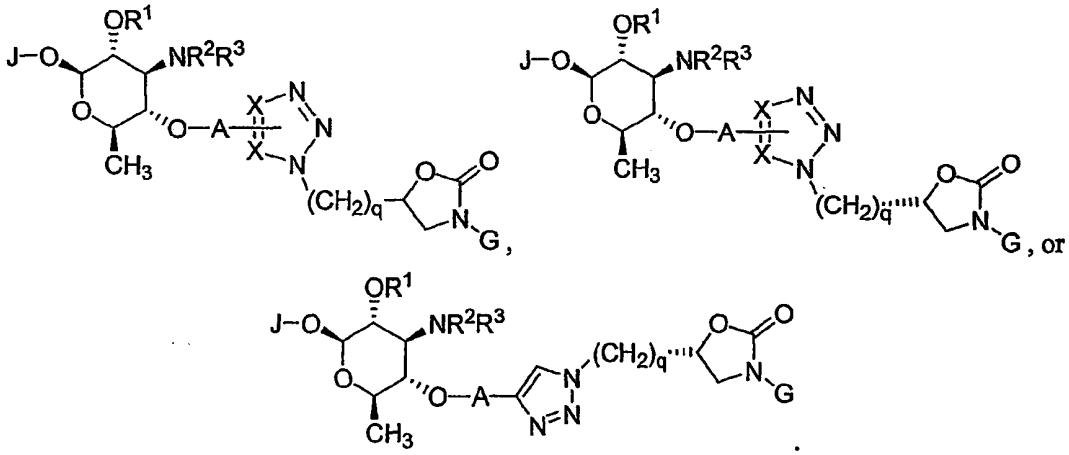
wherein A, D, G, J, R^1, R^2, R^3, R^4, X, Y, p, and q are as defined above.

In other embodiments, the invention provides compounds having the formula:

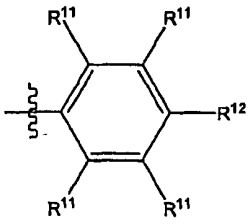


wherein O-A is $O-(CH_2)_r$, O-C(O), or $O-C(O)-(CH_2)_r$; r is 1, 2, 3, or 4; J is a macrolide; and G, R^1, R^2, R^3, R^4, X, Y, and q are as defined above.

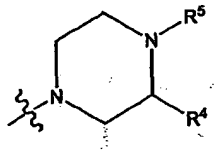
In still other embodiments, the invention provides compounds having the formula:



In certain embodiments of the foregoing compounds, G has the formula:

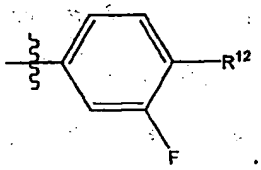


wherein R^{11} and R^{12} are as previously defined. In particular embodiments of these compounds, R^{12} is $-C(O)CH_3$. In other embodiments, R^{12} has the formula:

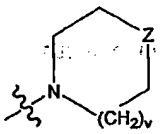


wherein R^4 and R^5 are as defined above. In certain embodiments of these compounds, R^5 is $-C(O)-CH_2-OH$. In other embodiments, R^4 is H.

In other embodiments, G has the formula:

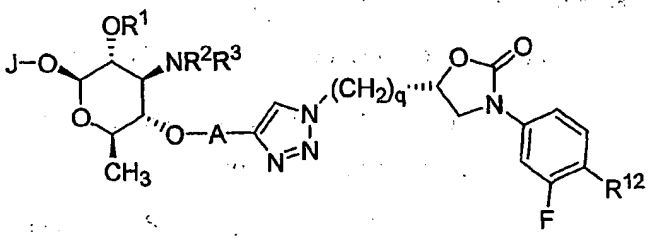


wherein R^{12} is as described above. In certain embodiments of these compounds, R^{12} is H. In other embodiments, R^{12} has the formula:

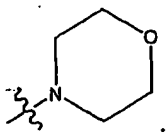


wherein Z is selected from the group consisting of O, NR^5, and $S(O)_t$; and v is 0, 1, 2, or 3. In particular embodiments, Z is O and v is 1.

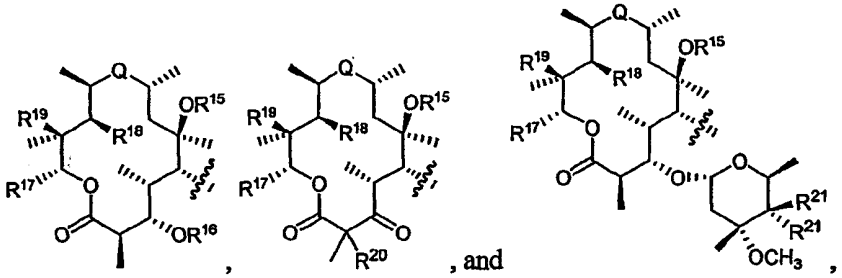
In certain embodiments, the invention provides compounds having the formula:



wherein O-A is $O-(CH_2)_r$, O-C(O), or $O-C(O)-(CH_2)_r$; r is 1, 2, 3, or 4; J is a macrolide; and R^1, R^2, R^3, R^{12}, and q are as defined above. In embodiments of these compounds, R^{12} is H or



In still other embodiments of the foregoing compounds, J is a macrolide. In certain embodiments of these compounds, the macrolide is selected from the group consisting of:



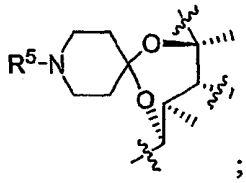
and pharmaceutically acceptable salts, esters and prodrugs thereof, wherein

Q is selected from the group consisting of:

$-NR^5CH_2-$, $-CH_2-NR^5-$, $-C(O)-$, $-C(=NR^5)-$, $-C(=NOR^5)-$, $-C(=N-NR^5R^5)-$, $-CH(OR^5)-$, and $-CH(NR^5R^5)-$;

R^{15} and R^{16} independently are selected from the group consisting of R^5 and a hydroxy protecting group;

alternatively R^{15} and R^{16}, taken together with the atoms to which they are bonded, form:



;

R^{17} is selected from the group consisting of:

a) C_{1-6} alkyl, b) C_{2-6} alkenyl, and c) C_{2-6} alkynyl;

wherein any of a) – c) optionally is substituted with one or more moieties selected from the group consisting of

i) $-OR^5$, ii) C_{3-14} saturated, unsaturated, or aromatic carbocycle, and iii) 3-14 membered saturated, unsaturated, or aromatic heterocycle containing one or more atoms selected from the group consisting of nitrogen, oxygen, and sulfur,

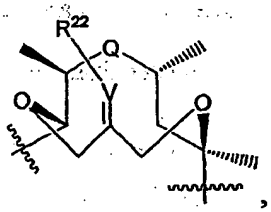
wherein any of ii) - iii) optionally is substituted with one or more R^4 groups;

R^{18} is selected from the group consisting of:

a) $-OR^{15}$, b) C_{1-6} alkyl , c) C_{2-6} alkenyl, d) C_{2-6} alkynyl, e) $-C(O)R^5$, and f) $-NR^5R^5$,

wherein any of b) - d) optionally is substituted with one or more R^4 groups;

alternatively, R^{15} and R^{18}, taken together with the atoms to which they are bonded, form:



wherein

V is CH or N, and

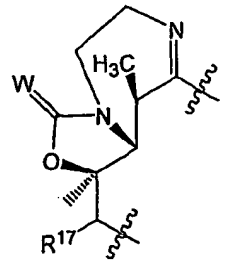
R^{22} is $-OR^5$, or R^5;

R^{19} is $-OR^{15}$;

alternatively, R^{18} and R^{19}, taken together with the atoms to which they are bonded, form a 5-membered ring by attachment to each other through a linker selected from the group consisting of:

$-OC(R^4)(R^4)O-$, $-OC(O)O-$, $-OC(O)NR^5-$, $-NR^5C(O)O-$, $-OC(O)NOR^5-$, $-N(OR^5)C(O)O-$, $-OC(O)N-NR^5R^5-$, $-N(NR^5R^5)C(O)O-$, $-OC(O)CHR^5-$, $-CHR^4C(O)O-$, $-OC(S)O-$, $-OC(S)NR^5-$, $-NR^5C(S)O-$, $-OC(S)NOR^5-$, $-N(OR^5)C(S)O-$, $-OC(S)N-NR^5R^5-$, $-N(NR^5R^5)C(S)O-$, $-OC(S)CHR^4-$, and $-CHR^4C(S)O-$;

alternatively, Q, R^{18}, and R^{19}, taken together with the atoms to which they are bonded, form:



wherein

W is O, NR^5, or NOR^5;

R^{20} is selected from the group consisting of:

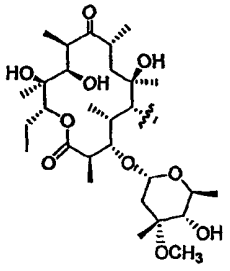
H, F, Cl, Br, and C_{1-6} alkyl;

R^{21}, at each occurrence, independently is selected from the group consisting of:

R^5, $-OR^{15}$, and $-NR^5R^5$;

alternatively, two R^{21} groups taken together are =O, =N-OR^5, or =N-NR^5R^5.

In particular embodiments, J is selected from the group consisting of: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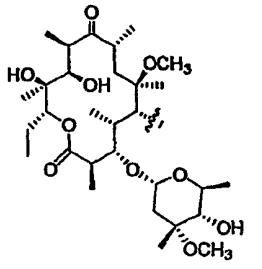
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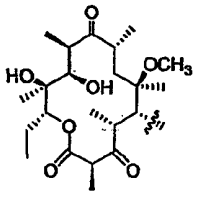
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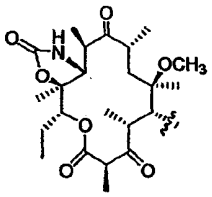
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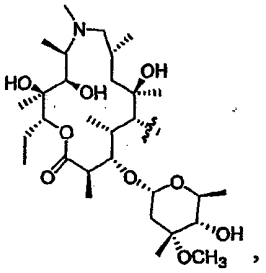
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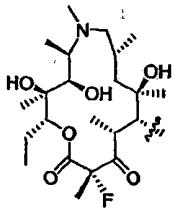
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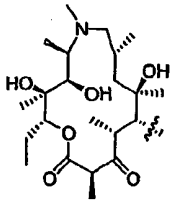
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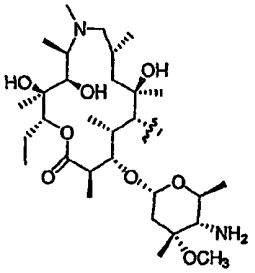
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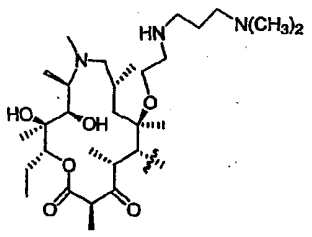
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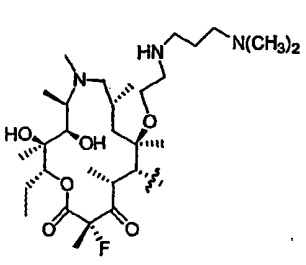
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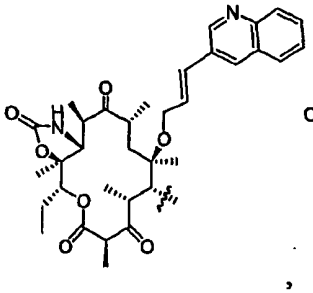
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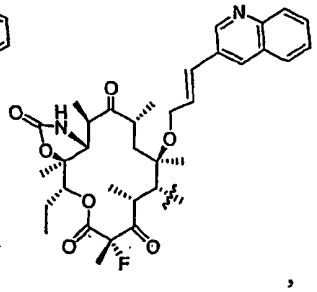
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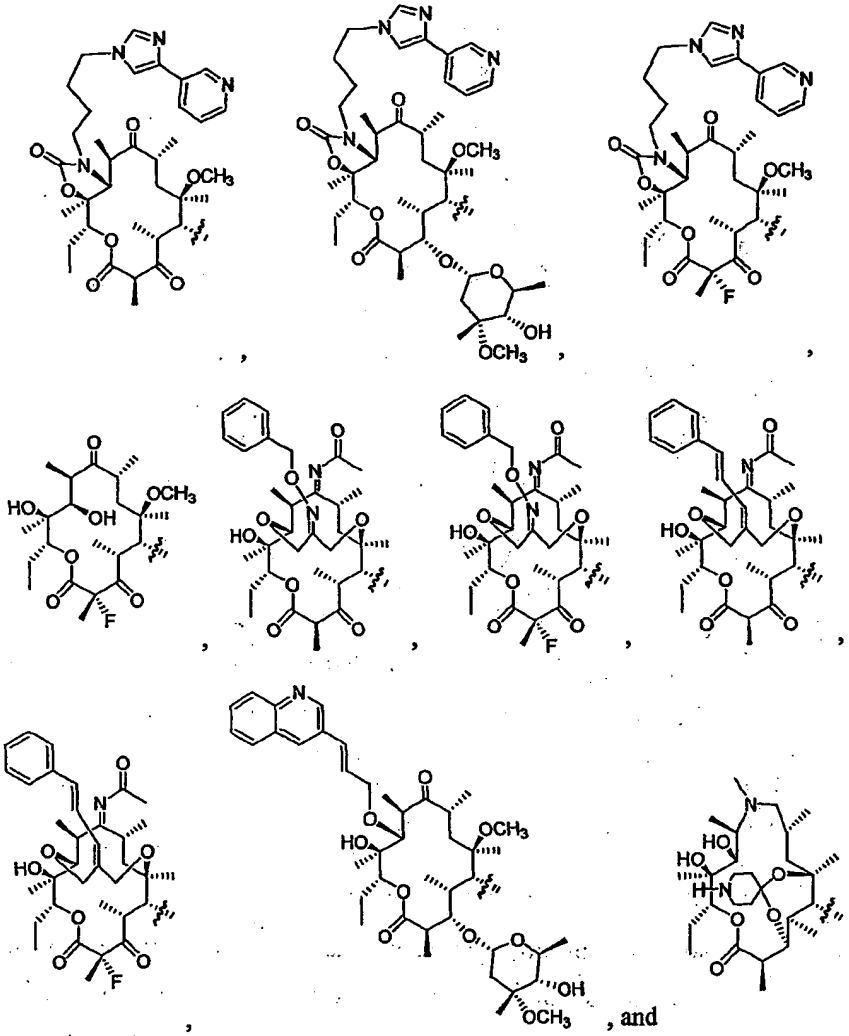
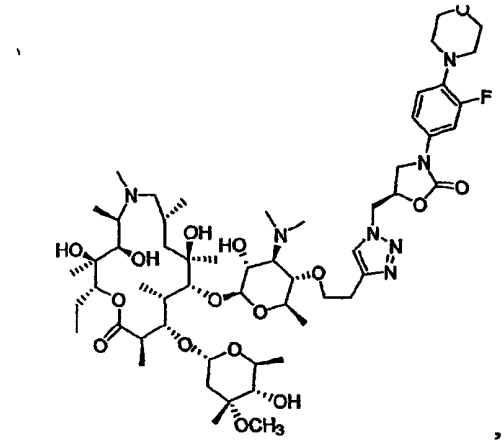
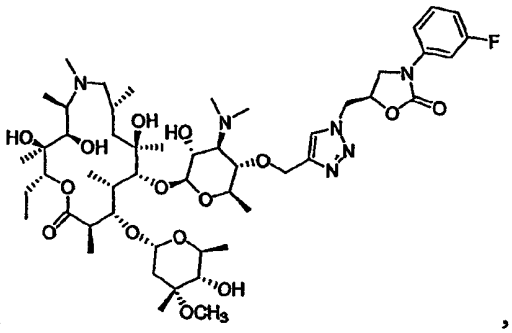
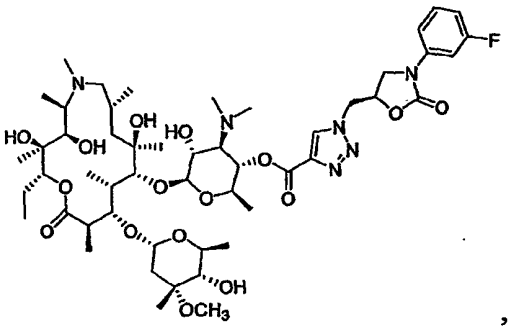
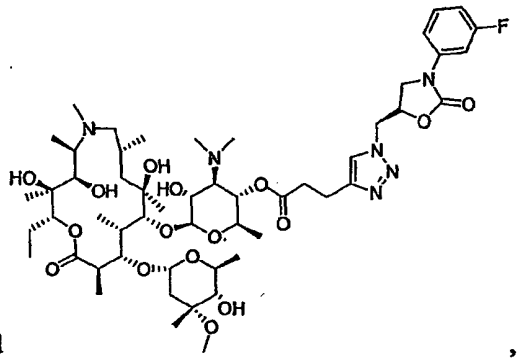


In other embodiments of the foregoing compounds, R^1 is H; R^2 is methyl; and R^3 is methyl.

Particular embodiments of the invention include:

, and

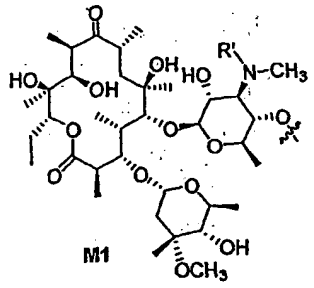
or a pharmaceutically acceptable salt, ester, or prodrug thereof.

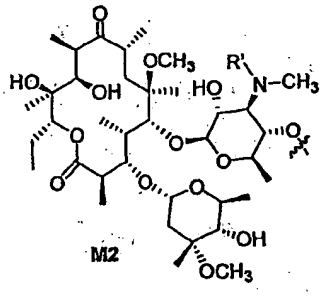
In another aspect, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of one or more of the foregoing compounds and a pharmaceutically acceptable carrier. In yet another aspect, the invention provides a method for treating a microbial infection, a fungal infection, a viral infection, a parasitic disease, a proliferative disease, an inflammatory disease, or a gastrointestinal motility disorder in a mammal, fish, or fowl by administering effective amounts of the compounds of the invention or pharmaceutical compositions of the invention, for example, via oral, parenteral or topical routes. In still another aspect, the invention provides methods for synthesizing any one of the foregoing compounds. In another aspect, the invention provides a medical device, for example, a medical stent, which contains or is coated with one or more of the foregoing compounds.

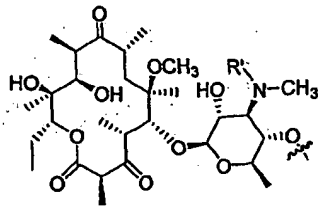
In another embodiment, the invention further provides a family of compounds comprising a heterocyclic side-chain linked via a heterocyclic linker to at least a portion of a macrolide. Exemplary macrolides, heterocyclic linkers, and heterocyclic side-chains useful in

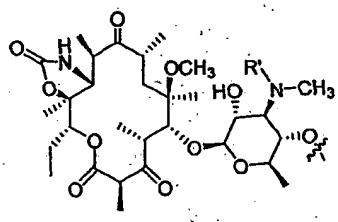
the synthesis of the compounds include, but are not limited to, the chemical moieties shown below:

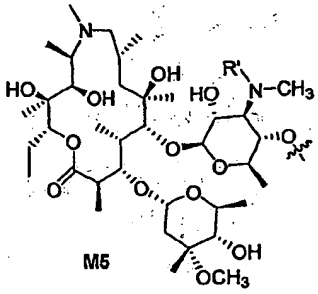
Macrolides


M1


M2


M3


M4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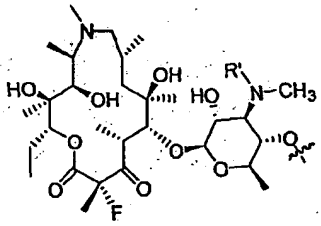
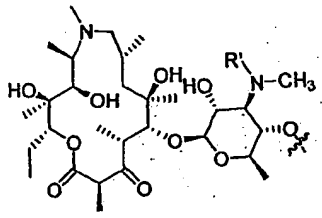
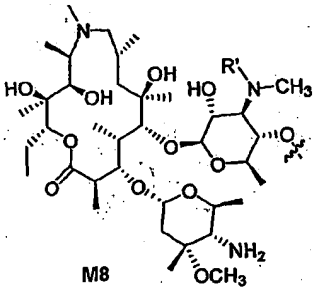
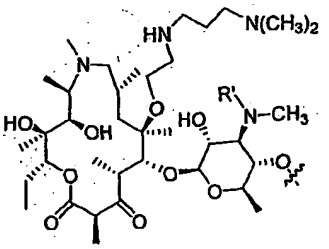
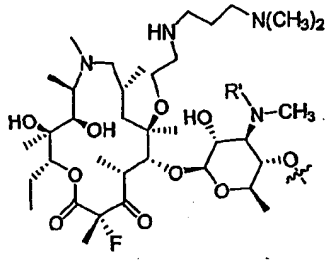

M6


M7


M8


M9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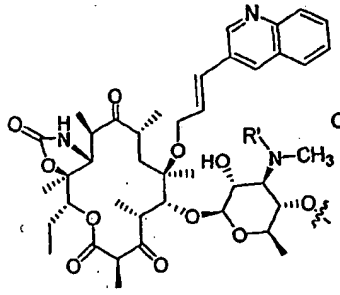
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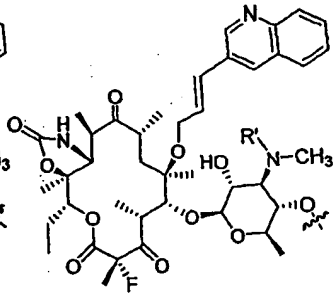
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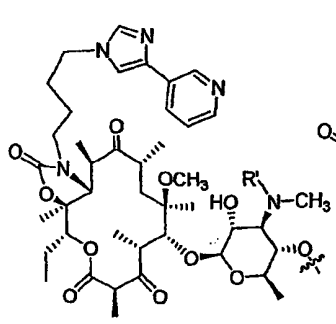
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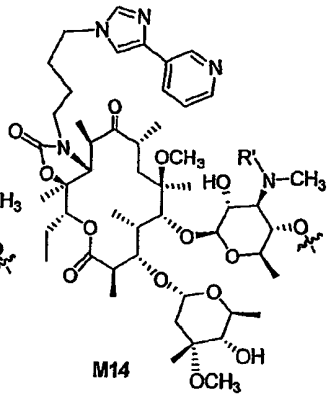
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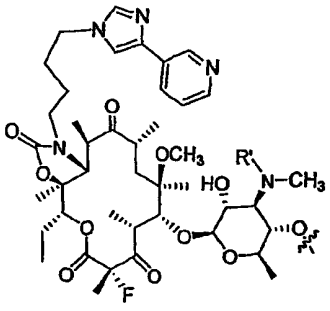
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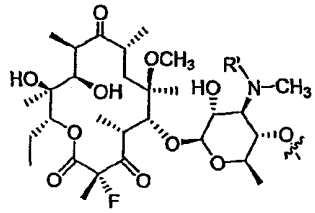
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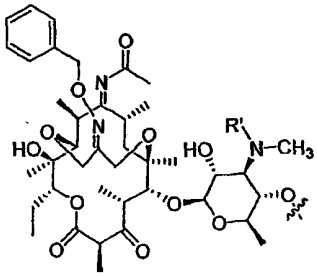
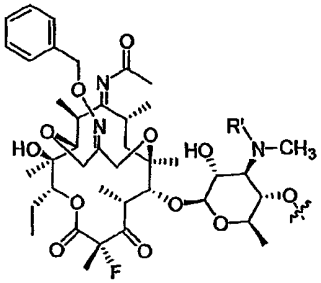

M17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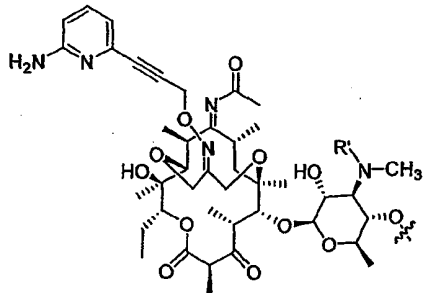
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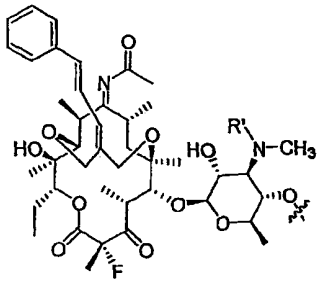
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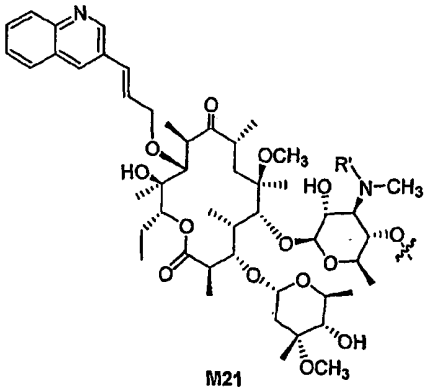
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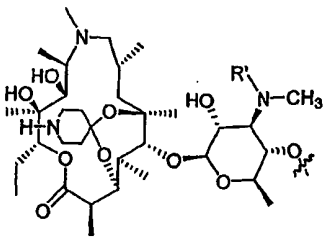
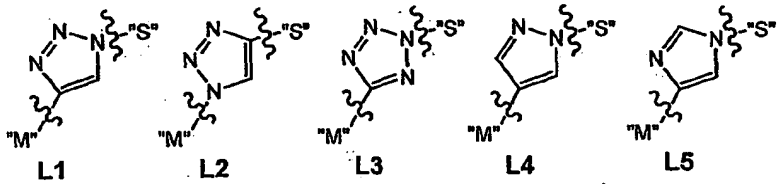

M22

For the above macrolides, R' can be either hydrogen or methyl.

Linkers

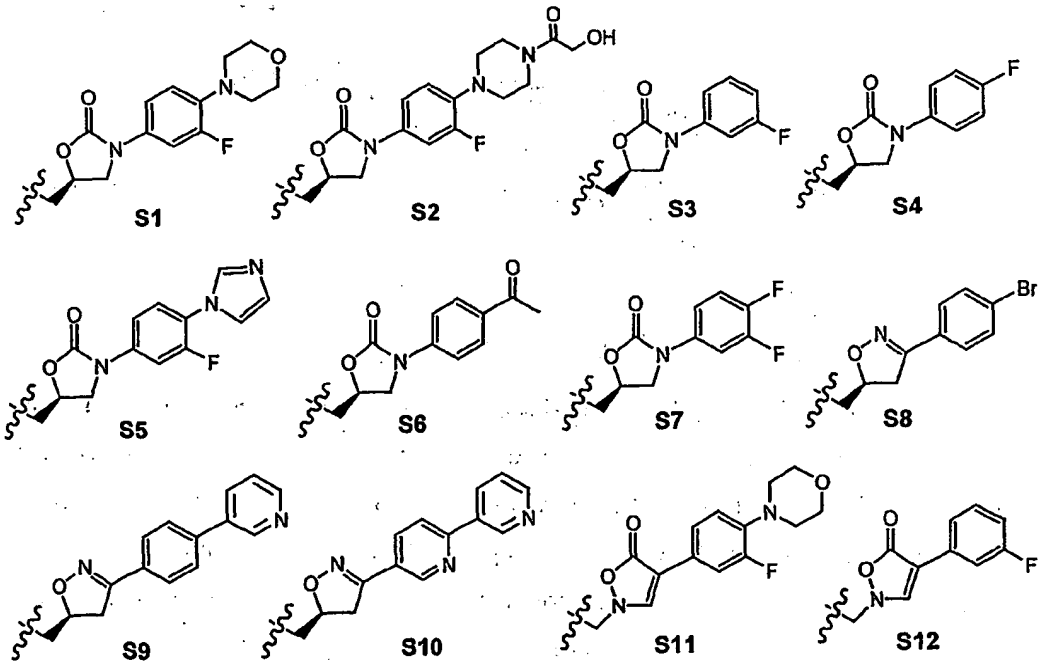


L1 L2 L3 L4 L5

L6 L7 L8 L9

For the above heterocyclic linkers, "M" and "S" are included to depict the orientation of the heterocyclic linker with respect to the other structures that define the compounds of the invention. More specifically, "M" denotes the portion of the compound that includes the macrolide moiety, and "S" denotes the portion of the compound that includes the heterocyclic side-chain moiety.

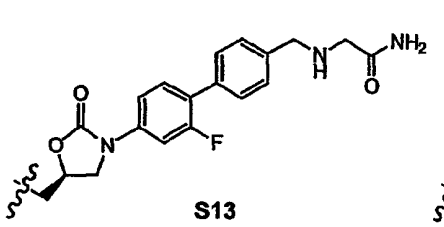
Side-Chains



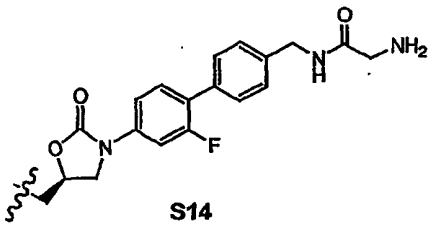
S1 S2 S3 S4

S5 S6 S7 S8

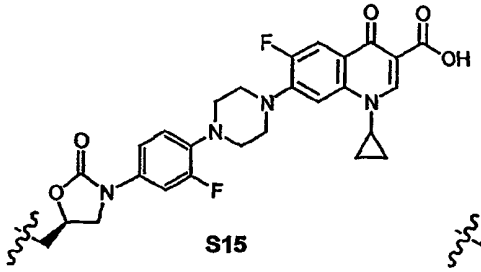
S9 S10 S11 S12



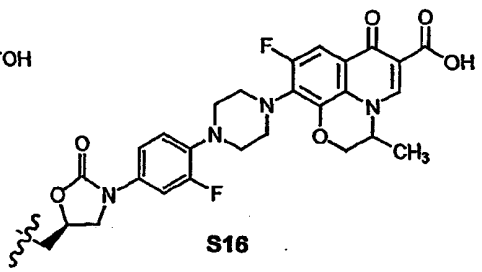
S13



S14

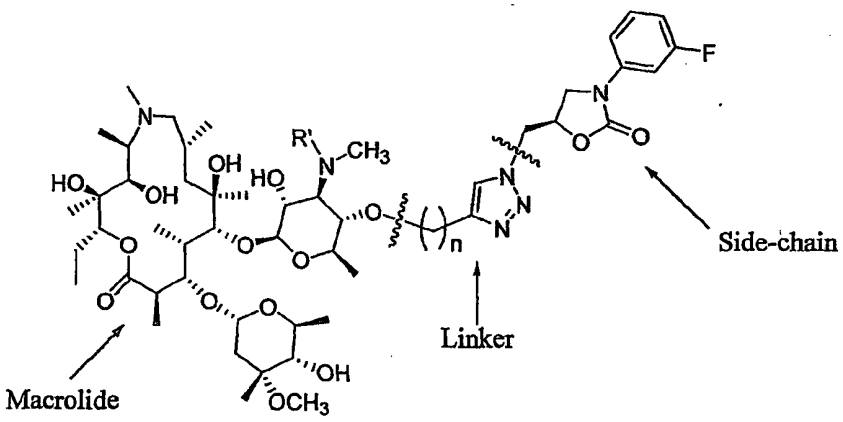


S15



S16

An exemplary scheme showing the linkage of a heterocyclic side-chain to a macrolide fragment via a heterocyclic linker is depicted below, where R' is hydrogen or methyl and n is 1, 2, 3, or 4:



The various heterocyclic side-chains may be linked via the heterocyclic linkers to the macrolides using conventional chemistries known in the art, such as those discussed below. By using the various combinations of chemical moieties provided, the skilled artisan may synthesize one or more of the exemplary compounds listed below in Table 2. For each set of examples, the lower case letter designations denote compounds where R' is hydrogen or methyl and n is 1, 2, 3, or 4. The R' and n values for each lower case letter designation are set forth in Table 1 below.

Table 1

Compound	R'	n
a	H	1
b	H	2
c	H	3
d	H	4
e	methyl	1
f	methyl	2
g	methyl	3
h	methyl	4

For example, as a guide to Table 2, compound **E1a** is the R' = H, n = 1 variant of the structure shown on the row 1 of the table, compound **E1b** is the R' = H, n = 2 derivative, and **E1e** is the R' = methyl, n = 1 derivative.

Table 2

Example	S Group	L Group	M Group
E1a-h	S1	L1	M1
E2a-h	S1	L2	M1
E3a-h	S1	L3	M1
E4a-h	S1	L4	M1
E5a-h	S1	L5	M1
E6a-h	S1	L6	M1
E7a-h	S1	L7	M1
E8a-h	S1	L8	M1
E9a-h	S1	L9	M1
E10a-h	S2	L1	M1
E11a-h	S2	L2	M1
E12a-h	S2	L3	M1
E13a-h	S2	L4	M1
E14a-h	S2	L5	M1
E15a-h	S2	L6	M1
E16a-h	S2	L7	M1
E17a-h	S2	L8	M1
E18a-h	S2	L9	M1
E19a-h	S3	L1	M1
E20a-h	S3	L2	M1
E21a-h	S3	L3	M1

Example	S Group	L Group	M Group
E22a-h	S3	L4	M1
E23a-h	S3	L5	M1
E24a-h	S3	L6	M1
E25a-h	S3	L7	M1
E26a-h	S3	L8	M1
E27a-h	S3	L9	M1
E28a-h	S4	L1	M1
E29a-h	S4	L2	M1
E30a-h	S4	L3	M1
E31a-h	S4	L4	M1
E32a-h	S4	L5	M1
E33a-h	S4	L6	M1
E34a-h	S4	L7	M1
E35a-h	S4	L8	M1
E36a-h	S4	L9	M1
E37a-h	S5	L1	M1
E38a-h	S5	L2	M1
E39a-h	S5	L3	M1
E40a-h	S5	L4	M1
E41a-h	S5	L5	M1
E42a-h	S5	L6	M1
E43a-h	S5	L7	M1
E44a-h	S5	L8	M1
E45a-h	S5	L9	M1
E46a-h	S6	L1	M1
E47a-h	S6	L2	M1
E48a-h	S6	L3	M1
E49a-h	S6	L4	M1
E50a-h	S6	L5	M1
E51a-h	S6	L6	M1
E52a-h	S6	L7	M1
E53a-h	S6	L8	M1
E54a-h	S6	L9	M1
E55a-h	S7	L1	M1
E56a-h	S7	L2	M1
E57a-h	S7	L3	M1
E58a-h	S7	L4	M1
E59a-h	S7	L5	M1
E60a-h	S7	L6	M1
E61a-h	S7	L7	M1
E62a-h	S7	L8	M1
E63a-h	S7	L9	M1
E64a-h	S8	L1	M1
E65a-h	S8	L2	M1
E66a-h	S8	L3	M1
E67a-h	S8	L4	M1
E68a-h	S8	L5	M1

Example	S Group	L Group	M Group
E69a-h	S8	L6	M1
E70a-h	S8	L7	M1
E71a-h	S8	L8	M1
E72a-h	S8	L9	M1
E73a-h	S9	L1	M1
E74a-h	S9	L2	M1
E75a-h	S9	L3	M1
E76a-h	S9	L4	M1
E77a-h	S9	L5	M1
E78a-h	S9	L6	M1
E79a-h	S9	L7	M1
E80a-h	S9	L8	M1
E81a-h	S9	L9	M1
E82a-h	S10	L1	M1
E83a-h	S10	L2	M1
E84a-h	S10	L3	M1
E85a-h	S10	L4	M1
E86a-h	S10	L5	M1
E87a-h	S10	L6	M1
E88a-h	S10	L7	M1
E89a-h	S10	L8	M1
E90a-h	S10	L9	M1
E91a-h	S11	L1	M1
E92a-h	S11	L2	M1
E93a-h	S11	L3	M1
E94a-h	S11	L4	M1
E95a-h	S11	L5	M1
E96a-h	S11	L6	M1
E97a-h	S11	L7	M1
E98a-h	S11	L8	M1
E99a-h	S11	L9	M1
E100a-h	S12	L1	M1
E101a-h	S12	L2	M1
E102a-h	S12	L3	M1
E103a-h	S12	L4	M1
E104a-h	S12	L5	M1
E105a-h	S12	L6	M1
E106a-h	S12	L7	M1
E107a-h	S12	L8	M1
E108a-h	S12	L9	M1
E109a-h	S13	L1	M1
E110a-h	S13	L2	M1
E111a-h	S13	L3	M1
E112a-h	S13	L4	M1
E113a-h	S13	L5	M1
E114a-h	S13	L6	M1
E115a-h	S13	L7	M1

Example	S Group	L Group	M Group
E116a-h	S13	L8	M1
E117a-h	S13	L9	M1
E118a-h	S14	L1	M1
E119a-h	S14	L2	M1
E120a-h	S14	L3	M1
E121a-h	S14	L4	M1
E122a-h	S14	L5	M1
E123a-h	S14	L6	M1
E124a-h	S14	L7	M1
E125a-h	S14	L8	M1
E126a-h	S14	L9	M1
E127a-h	S15	L1	M1
E128a-h	S15	L2	M1
E129a-h	S15	L3	M1
E130a-h	S15	L4	M1
E131a-h	S15	L5	M1
E132a-h	S15	L6	M1
E133a-h	S15	L7	M1
E134a-h	S15	L8	M1
E135a-h	S15	L9	M1
E136a-h	S16	L1	M1
E137a-h	S16	L2	M1
E138a-h	S16	L3	M1
E139a-h	S16	L4	M1
E140a-h	S16	L5	M1
E141a-h	S16	L6	M1
E142a-h	S16	L7	M1
E143a-h	S16	L8	M1
E144a-h	S16	L9	M1
E145a-h	S1	L1	M2
E146a-h	S1	L2	M2
E147a-h	S1	L3	M2
E148a-h	S1	L4	M2
E149a-h	S1	L5	M2
E150a-h	S1	L6	M2
E151a-h	S1	L7	M2
E152a-h	S1	L8	M2
E153a-h	S1	L9	M2
E154a-h	S2	L1	M2
E155a-h	S2	L2	M2
E156a-h	S2	L3	M2
E157a-h	S2	L4	M2
E158a-h	S2	L5	M2
E159a-h	S2	L6	M2
E160a-h	S2	L7	M2
E161a-h	S2	L8	M2
E162a-h	S2	L9	M2

Example	S Group	L Group	M Group
E163a-h	S3	L1	M2
E164a-h	S3	L2	M2
E165a-h	S3	L3	M2
E166a-h	S3	L4	M2
E167a-h	S3	L5	M2
E168a-h	S3	L6	M2
E169a-h	S3	L7	M2
E170a-h	S3	L8	M2
E171a-h	S3	L9	M2
E172a-h	S4	L1	M2
E173a-h	S4	L2	M2
E174a-h	S4	L3	M2
E175a-h	S4	L4	M2
E176a-h	S4	L5	M2
E177a-h	S4	L6	M2
E178a-h	S4	L7	M2
E179a-h	S4	L8	M2
E180a-h	S4	L9	M2
E181a-h	S5	L1	M2
E182a-h	S5	L2	M2
E183a-h	S5	L3	M2
E184a-h	S5	L4	M2
E185a-h	S5	L5	M2
E186a-h	S5	L6	M2
E187a-h	S5	L7	M2
E188a-h	S5	L8	M2
E189a-h	S5	L9	M2
E190a-h	S6	L1	M2
E191a-h	S6	L2	M2
E192a-h	S6	L3	M2
E193a-h	S6	L4	M2
E194a-h	S6	L5	M2
E195a-h	S6	L6	M2
E196a-h	S6	L7	M2
E197a-h	S6	L8	M2
E198a-h	S6	L9	M2
E199a-h	S7	L1	M2
E200a-h	S7	L2	M2
E201a-h	S7	L3	M2
E202a-h	S7	L4	M2
E203a-h	S7	L5	M2
E204a-h	S7	L6	M2
E205a-h	S7	L7	M2
E206a-h	S7	L8	M2
E207a-h	S7	L9	M2
E208a-h	S8	L1	M2
E209a-h	S8	L2	M2

Example	S Group	L Group	M Group
E210a-h	S8	L3	M2
E211a-h	S8	L4	M2
E212a-h	S8	L5	M2
E213a-h	S8	L6	M2
E214a-h	S8	L7	M2
E215a-h	S8	L8	M2
E216a-h	S8	L9	M2
E217a-h	S9	L1	M2
E218a-h	S9	L2	M2
E219a-h	S9	L3	M2
E220a-h	S9	L4	M2
E221a-h	S9	L5	M2
E222a-h	S9	L6	M2
E223a-h	S9	L7	M2
E224a-h	S9	L8	M2
E225a-h	S9	L9	M2
E226a-h	S10	L1	M2
E227a-h	S10	L2	M2
E228a-h	S10	L3	M2
E229a-h	S10	L4	M2
E230a-h	S10	L5	M2
E231a-h	S10	L6	M2
E232a-h	S10	L7	M2
E233a-h	S10	L8	M2
E234a-h	S10	L9	M2
E235a-h	S11	L1	M2
E236a-h	S11	L2	M2
E237a-h	S11	L3	M2
E238a-h	S11	L4	M2
E239a-h	S11	L5	M2
E240a-h	S11	L6	M2
E241a-h	S11	L7	M2
E242a-h	S11	L8	M2
E243a-h	S11	L9	M2
E244a-h	S12	L1	M2
E245a-h	S12	L2	M2
E246a-h	S12	L3	M2
E247a-h	S12	L4	M2
E248a-h	S12	L5	M2
E249a-h	S12	L6	M2
E250a-h	S12	L7	M2
E251a-h	S12	L8	M2
E252a-h	S12	L9	M2
E253a-h	S13	L1	M2
E254a-h	S13	L2	M2
E255a-h	S13	L3	M2
E256a-h	S13	L4	M2

Example	S Group	L Group	M Group
E257a-h	S13	L5	M2
E258a-h	S13	L6	M2
E259a-h	S13	L7	M2
E260a-h	S13	L8	M2
E261a-h	S13	L9	M2
E262a-h	S14	L1	M2
E263a-h	S14	L2	M2
E264a-h	S14	L3	M2
E265a-h	S14	L4	M2
E266a-h	S14	L5	M2
E267a-h	S14	L6	M2
E268a-h	S14	L7	M2
E269a-h	S14	L8	M2
E270a-h	S14	L9	M2
E271a-h	S15	L1	M2
E272a-h	S15	L2	M2
E273a-h	S15	L3	M2
E274a-h	S15	L4	M2
E275a-h	S15	L5	M2
E276a-h	S15	L6	M2
E277a-h	S15	L7	M2
E278a-h	S15	L8	M2
E279a-h	S15	L9	M2
E280a-h	S16	L1	M2
E281a-h	S16	L2	M2
E282a-h	S16	L3	M2
E283a-h	S16	L4	M2
E284a-h	S16	L5	M2
E285a-h	S16	L6	M2
E286a-h	S16	L7	M2
E287a-h	S16	L8	M2
E288a-h	S16	L9	M2
E289a-h	S1	L1	M3
E290a-h	S1	L2	M3
E291a-h	S1	L3	M3
E292a-h	S1	L4	M3
E293a-h	S1	L5	M3
E294a-h	S1	L6	M3
E295a-h	S1	L7	M3
E296a-h	S1	L8	M3
E297a-h	S1	L9	M3
E298a-h	S2	L1	M3
E299a-h	S2	L2	M3
E300a-h	S2	L3	M3
E301a-h	S2	L4	M3
E302a-h	S2	L5	M3
E303a-h	S2	L6	M3

Example	S Group	L Group	M Group
E304a-h	S2	L7	M3
E305a-h	S2	L8	M3
E306a-h	S2	L9	M3
E307a-h	S3	L1	M3
E308a-h	S3	L2	M3
E309a-h	S3	L3	M3
E310a-h	S3	L4	M3
E311a-h	S3	L5	M3
E312a-h	S3	L6	M3
E313a-h	S3	L7	M3
E314a-h	S3	L8	M3
E315a-h	S3	L9	M3
E316a-h	S4	L1	M3
E317a-h	S4	L2	M3
E318a-h	S4	L3	M3
E319a-h	S4	L4	M3
E320a-h	S4	L5	M3
E321a-h	S4	L6	M3
E322a-h	S4	L7	M3
E323a-h	S4	L8	M3
E324a-h	S4	L9	M3
E325a-h	S5	L1	M3
E326a-h	S5	L2	M3
E327a-h	S5	L3	M3
E328a-h	S5	L4	M3
E329a-h	S5	L5	M3
E330a-h	S5	L6	M3
E331a-h	S5	L7	M3
E332a-h	S5	L8	M3
E333a-h	S5	L9	M3
E334a-h	S6	L1	M3
E335a-h	S6	L2	M3
E336a-h	S6	L3	M3
E337a-h	S6	L4	M3
E338a-h	S6	L5	M3
E339a-h	S6	L6	M3
E340a-h	S6	L7	M3
E341a-h	S6	L8	M3
E342a-h	S6	L9	M3
E343a-h	S7	L1	M3
E344a-h	S7	L2	M3
E345a-h	S7	L3	M3
E346a-h	S7	L4	M3
E347a-h	S7	L5	M3
E348a-h	S7	L6	M3
E349a-h	S7	L7	M3
E350a-h	S7	L8	M3

Example	S Group	L Group	M Group
E351a-h	S7	L9	M3
E352a-h	S8	L1	M3
E353a-h	S8	L2	M3
E354a-h	S8	L3	M3
E355a-h	S8	L4	M3
E356a-h	S8	L5	M3
E357a-h	S8	L6	M3
E358a-h	S8	L7	M3
E359a-h	S8	L8	M3
E360a-h	S8	L9	M3
E361a-h	S9	L1	M3
E362a-h	S9	L2	M3
E363a-h	S9	L3	M3
E364a-h	S9	L4	M3
E365a-h	S9	L5	M3
E366a-h	S9	L6	M3
E367a-h	S9	L7	M3
E368a-h	S9	L8	M3
E369a-h	S9	L9	M3
E370a-h	S10	L1	M3
E371a-h	S10	L2	M3
E372a-h	S10	L3	M3
E373a-h	S10	L4	M3
E374a-h	S10	L5	M3
E375a-h	S10	L6	M3
E376a-h	S10	L7	M3
E377a-h	S10	L8	M3
E378a-h	S10	L9	M3
E379a-h	S11	L1	M3
E380a-h	S11	L2	M3
E381a-h	S11	L3	M3
E382a-h	S11	L4	M3
E383a-h	S11	L5	M3
E384a-h	S11	L6	M3
E385a-h	S11	L7	M3
E386a-h	S11	L8	M3
E387a-h	S11	L9	M3
E388a-h	S12	L1	M3
E389a-h	S12	L2	M3
E390a-h	S12	L3	M3
E391a-h	S12	L4	M3
E392a-h	S12	L5	M3
E393a-h	S12	L6	M3
E394a-h	S12	L7	M3
E395a-h	S12	L8	M3
E396a-h	S12	L9	M3
E397a-h	S13	L1	M3

Example	S Group	L Group	M Group
E398a-h	S13	L2	M3
E399a-h	S13	L3	M3
E400a-h	S13	L4	M3
E401a-h	S13	L5	M3
E402a-h	S13	L6	M3
E403a-h	S13	L7	M3
E404a-h	S13	L8	M3
E405a-h	S13	L9	M3
E406a-h	S14	L1	M3
E407a-h	S14	L2	M3
E408a-h	S14	L3	M3
E409a-h	S14	L4	M3
E410a-h	S14	L5	M3
E411a-h	S14	L6	M3
E412a-h	S14	L7	M3
E413a-h	S14	L8	M3
E414a-h	S14	L9	M3
E415a-h	S15	L1	M3
E416a-h	S15	L2	M3
E417a-h	S15	L3	M3
E418a-h	S15	L4	M3
E419a-h	S15	L5	M3
E420a-h	S15	L6	M3
E421a-h	S15	L7	M3
E422a-h	S15	L8	M3
E423a-h	S15	L9	M3
E424a-h	S16	L1	M3
E425a-h	S16	L2	M3
E426a-h	S16	L3	M3
E427a-h	S16	L4	M3
E428a-h	S16	L5	M3
E429a-h	S16	L6	M3
E430a-h	S16	L7	M3
E431a-h	S16	L8	M3
E432a-h	S16	L9	M3
E433a-h	S1	L1	M4
E434a-h	S1	L2	M4
E435a-h	S1	L3	M4
E436a-h	S1	L4	M4
E437a-h	S1	L5	M4
E438a-h	S1	L6	M4
E439a-h	S1	L7	M4
E440a-h	S1	L8	M4
E441a-h	S1	L9	M4
E442a-h	S2	L1	M4
E443a-h	S2	L2	M4
E444a-h	S2	L3	M4

Example	S Group	L Group	M Group
E445a-h	S2	L4	M4
E446a-h	S2	L5	M4
E447a-h	S2	L6	M4
E448a-h	S2	L7	M4
E449a-h	S2	L8	M4
E450a-h	S2	L9	M4
E451a-h	S3	L1	M4
E452a-h	S3	L2	M4
E453a-h	S3	L3	M4
E454a-h	S3	L4	M4
E455a-h	S3	L5	M4
E456a-h	S3	L6	M4
E457a-h	S3	L7	M4
E458a-h	S3	L8	M4
E459a-h	S3	L9	M4
E460a-h	S4	L1	M4
E461a-h	S4	L2	M4
E462a-h	S4	L3	M4
E463a-h	S4	L4	M4
E464a-h	S4	L5	M4
E465a-h	S4	L6	M4
E466a-h	S4	L7	M4
E467a-h	S4	L8	M4
E468a-h	S4	L9	M4
E469a-h	S5	L1	M4
E470a-h	S5	L2	M4
E471a-h	S5	L3	M4
E472a-h	S5	L4	M4
E473a-h	S5	L5	M4
E474a-h	S5	L6	M4
E475a-h	S5	L7	M4
E476a-h	S5	L8	M4
E477a-h	S5	L9	M4
E478a-h	S6	L1	M4
E479a-h	S6	L2	M4
E480a-h	S6	L3	M4
E481a-h	S6	L4	M4
E482a-h	S6	L5	M4
E483a-h	S6	L6	M4
E484a-h	S6	L7	M4
E485a-h	S6	L8	M4
E486a-h	S6	L9	M4
E487a-h	S7	L1	M4
E488a-h	S7	L2	M4
E489a-h	S7	L3	M4
E490a-h	S7	L4	M4
E491a-h	S7	L5	M4

Example	S Group	L Group	M Group
E492a-h	S7	L6	M4
E493a-h	S7	L7	M4
E494a-h	S7	L8	M4
E495a-h	S7	L9	M4
E496a-h	S8	L1	M4
E497a-h	S8	L2	M4
E498a-h	S8	L3	M4
E499a-h	S8	L4	M4
E500a-h	S8	L5	M4
E501a-h	S8	L6	M4
E502a-h	S8	L7	M4
E503a-h	S8	L8	M4
E504a-h	S8	L9	M4
E505a-h	S9	L1	M4
E506a-h	S9	L2	M4
E507a-h	S9	L3	M4
E508a-h	S9	L4	M4
E509a-h	S9	L5	M4
E510a-h	S9	L6	M4
E511a-h	S9	L7	M4
E512a-h	S9	L8	M4
E513a-h	S9	L9	M4
E514a-h	S10	L1	M4
E515a-h	S10	L2	M4
E516a-h	S10	L3	M4
E517a-h	S10	L4	M4
E518a-h	S10	L5	M4
E519a-h	S10	L6	M4
E520a-h	S10	L7	M4
E521a-h	S10	L8	M4
E522a-h	S10	L9	M4
E523a-h	S11	L1	M4
E524a-h	S11	L2	M4
E525a-h	S11	L3	M4
E526a-h	S11	L4	M4
E527a-h	S11	L5	M4
E528a-h	S11	L6	M4
E529a-h	S11	L7	M4
E530a-h	S11	L8	M4
E531a-h	S11	L9	M4
E532a-h	S12	L1	M4
E533a-h	S12	L2	M4
E534a-h	S12	L3	M4
E535a-h	S12	L4	M4
E536a-h	S12	L5	M4
E537a-h	S12	L6	M4
E538a-h	S12	L7	M4

Example	S Group	L Group	M Group
E539a-h	S12	L8	M4
E540a-h	S12	L9	M4
E541a-h	S13	L1	M4
E542a-h	S13	L2	M4
E543a-h	S13	L3	M4
E544a-h	S13	L4	M4
E545a-h	S13	L5	M4
E546a-h	S13	L6	M4
E547a-h	S13	L7	M4
E548a-h	S13	L8	M4
E549a-h	S13	L9	M4
E550a-h	S14	L1	M4
E551a-h	S14	L2	M4
E552a-h	S14	L3	M4
E553a-h	S14	L4	M4
E554a-h	S14	L5	M4
E555a-h	S14	L6	M4
E556a-h	S14	L7	M4
E557a-h	S14	L8	M4
E558a-h	S14	L9	M4
E559a-h	S15	L1	M4
E560a-h	S15	L2	M4
E561a-h	S15	L3	M4
E562a-h	S15	L4	M4
E563a-h	S15	L5	M4
E564a-h	S15	L6	M4
E565a-h	S15	L7	M4
E566a-h	S15	L8	M4
E567a-h	S15	L9	M4
E568a-h	S16	L1	M4
E569a-h	S16	L2	M4
E570a-h	S16	L3	M4
E571a-h	S16	L4	M4
E572a-h	S16	L5	M4
E573a-h	S16	L6	M4
E574a-h	S16	L7	M4
E575a-h	S16	L8	M4
E576a-h	S16	L9	M4
E577a-h	S1	L1	M5
E578a-h	S1	L2	M5
E579a-h	S1	L3	M5
E580a-h	S1	L4	M5
E581a-h	S1	L5	M5
E582a-h	S1	L6	M5
E583a-h	S1	L7	M5
E584a-h	S1	L8	M5
E585a-h	S1	L9	M5

Example	S Group	L Group	M Group
E586a-h	S2	L1	M5
E587a-h	S2	L2	M5
E588a-h	S2	L3	M5
E589a-h	S2	L4	M5
E590a-h	S2	L5	M5
E591a-h	S2	L6	M5
E592a-h	S2	L7	M5
E593a-h	S2	L8	M5
E594a-h	S2	L9	M5
E595a-h	S3	L1	M5
E596a-h	S3	L2	M5
E597a-h	S3	L3	M5
E598a-h	S3	L4	M5
E599a-h	S3	L5	M5
E600a-h	S3	L6	M5
E601a-h	S3	L7	M5
E602a-h	S3	L8	M5
E603a-h	S3	L9	M5
E604a-h	S4	L1	M5
E605a-h	S4	L2	M5
E606a-h	S4	L3	M5
E607a-h	S4	L4	M5
E608a-h	S4	L5	M5
E609a-h	S4	L6	M5
E610a-h	S4	L7	M5
E611a-h	S4	L8	M5
E612a-h	S4	L9	M5
E613a-h	S5	L1	M5
E614a-h	S5	L2	M5
E615a-h	S5	L3	M5
E616a-h	S5	L4	M5
E617a-h	S5	L5	M5
E618a-h	S5	L6	M5
E619a-h	S5	L7	M5
E620a-h	S5	L8	M5
E621a-h	S5	L9	M5
E622a-h	S6	L1	M5
E623a-h	S6	L2	M5
E624a-h	S6	L3	M5
E625a-h	S6	L4	M5
E626a-h	S6	L5	M5
E627a-h	S6	L6	M5
E628a-h	S6	L7	M5
E629a-h	S6	L8	M5
E630a-h	S6	L9	M5
E631a-h	S7	L1	M5
E632a-h	S7	L2	M5

Example	S Group	L Group	M Group
E633a-h	S7	L3	M5
E634a-h	S7	L4	M5
E635a-h	S7	L5	M5
E636a-h	S7	L6	M5
E637a-h	S7	L7	M5
E638a-h	S7	L8	M5
E639a-h	S7	L9	M5
E640a-h	S8	L1	M5
E641a-h	S8	L2	M5
E642a-h	S8	L3	M5
E643a-h	S8	L4	M5
E644a-h	S8	L5	M5
E645a-h	S8	L6	M5
E646a-h	S8	L7	M5
E647a-h	S8	L8	M5
E648a-h	S8	L9	M5
E649a-h	S9	L1	M5
E650a-h	S9	L2	M5
E651a-h	S9	L3	M5
E652a-h	S9	L4	M5
E653a-h	S9	L5	M5
E654a-h	S9	L6	M5
E655a-h	S9	L7	M5
E656a-h	S9	L8	M5
E657a-h	S9	L9	M5
E658a-h	S10	L1	M5
E659a-h	S10	L2	M5
E660a-h	S10	L3	M5
E661a-h	S10	L4	M5
E662a-h	S10	L5	M5
E663a-h	S10	L6	M5
E664a-h	S10	L7	M5
E665a-h	S10	L8	M5
E666a-h	S10	L9	M5
E667a-h	S11	L1	M5
E668a-h	S11	L2	M5
E669a-h	S11	L3	M5
E670a-h	S11	L4	M5
E671a-h	S11	L5	M5
E672a-h	S11	L6	M5
E673a-h	S11	L7	M5
E674a-h	S11	L8	M5
E675a-h	S11	L9	M5
E676a-h	S12	L1	M5
E677a-h	S12	L2	M5
E678a-h	S12	L3	M5
E679a-h	S12	L4	M5

Example	S Group	L Group	M Group
E680a-h	S12	L5	M5
E681a-h	S12	L6	M5
E682a-h	S12	L7	M5
E683a-h	S12	L8	M5
E684a-h	S12	L9	M5
E685a-h	S13	L1	M5
E686a-h	S13	L2	M5
E687a-h	S13	L3	M5
E688a-h	S13	L4	M5
E689a-h	S13	L5	M5
E690a-h	S13	L6	M5
E691a-h	S13	L7	M5
E692a-h	S13	L8	M5
E693a-h	S13	L9	M5
E694a-h	S14	L1	M5
E695a-h	S14	L2	M5
E696a-h	S14	L3	M5
E697a-h	S14	L4	M5
E698a-h	S14	L5	M5
E699a-h	S14	L6	M5
E700a-h	S14	L7	M5
E701a-h	S14	L8	M5
E702a-h	S14	L9	M5
E703a-h	S15	L1	M5
E704a-h	S15	L2	M5
E705a-h	S15	L3	M5
E706a-h	S15	L4	M5
E707a-h	S15	L5	M5
E708a-h	S15	L6	M5
E709a-h	S15	L7	M5
E710a-h	S15	L8	M5
E711a-h	S15	L9	M5
E712a-h	S16	L1	M5
E713a-h	S16	L2	M5
E714a-h	S16	L3	M5
E715a-h	S16	L4	M5
E716a-h	S16	L5	M5
E717a-h	S16	L6	M5
E718a-h	S16	L7	M5
E719a-h	S16	L8	M5
E720a-h	S16	L9	M5
E721a-h	S1	L1	M6
E722a-h	S1	L2	M6
E723a-h	S1	L3	M6
E724a-h	S1	L4	M6
E725a-h	S1	L5	M6
E726a-h	S1	L6	M6

Example	S Group	L Group	M Group
E727a-h	S1	L7	M6
E728a-h	S1	L8	M6
E729a-h	S1	L9	M6
E730a-h	S2	L1	M6
E731a-h	S2	L2	M6
E732a-h	S2	L3	M6
E733a-h	S2	L4	M6
E734a-h	S2	L5	M6
E735a-h	S2	L6	M6
E736a-h	S2	L7	M6
E737a-h	S2	L8	M6
E738a-h	S2	L9	M6
E739a-h	S3	L1	M6
E740a-h	S3	L2	M6
E741a-h	S3	L3	M6
E742a-h	S3	L4	M6
E743a-h	S3	L5	M6
E744a-h	S3	L6	M6
E745a-h	S3	L7	M6
E746a-h	S3	L8	M6
E747a-h	S3	L9	M6
E748a-h	S4	L1	M6
E749a-h	S4	L2	M6
E750a-h	S4	L3	M6
E751a-h	S4	L4	M6
E752a-h	S4	L5	M6
E753a-h	S4	L6	M6
E754a-h	S4	L7	M6
E755a-h	S4	L8	M6
E756a-h	S4	L9	M6
E757a-h	S5	L1	M6
E758a-h	S5	L2	M6
E759a-h	S5	L3	M6
E760a-h	S5	L4	M6
E761a-h	S5	L5	M6
E762a-h	S5	L6	M6
E763a-h	S5	L7	M6
E764a-h	S5	L8	M6
E765a-h	S5	L9	M6
E766a-h	S6	L1	M6
E767a-h	S6	L2	M6
E768a-h	S6	L3	M6
E769a-h	S6	L4	M6
E770a-h	S6	L5	M6
E771a-h	S6	L6	M6
E772a-h	S6	L7	M6
E773a-h	S6	L8	M6

Example	S Group	L Group	M Group
E774a-h	S6	L9	M6
E775a-h	S7	L1	M6
E776a-h	S7	L2	M6
E777a-h	S7	L3	M6
E778a-h	S7	L4	M6
E779a-h	S7	L5	M6
E780a-h	S7	L6	M6
E781a-h	S7	L7	M6
E782a-h	S7	L8	M6
E783a-h	S7	L9	M6
E784a-h	S8	L1	M6
E785a-h	S8	L2	M6
E786a-h	S8	L3	M6
E787a-h	S8	L4	M6
E788a-h	S8	L5	M6
E789a-h	S8	L6	M6
E790a-h	S8	L7	M6
E791a-h	S8	L8	M6
E792a-h	S8	L9	M6
E793a-h	S9	L1	M6
E794a-h	S9	L2	M6
E795a-h	S9	L3	M6
E796a-h	S9	L4	M6
E797a-h	S9	L5	M6
E798a-h	S9	L6	M6
E799a-h	S9	L7	M6
E800a-h	S9	L8	M6
E801a-h	S9	L9	M6
E802a-h	S10	L1	M6
E803a-h	S10	L2	M6
E804a-h	S10	L3	M6
E805a-h	S10	L4	M6
E806a-h	S10	L5	M6
E807a-h	S10	L6	M6
E808a-h	S10	L7	M6
E809a-h	S10	L8	M6
E810a-h	S10	L9	M6
E811a-h	S11	L1	M6
E812a-h	S11	L2	M6
E813a-h	S11	L3	M6
E814a-h	S11	L4	M6
E815a-h	S11	L5	M6
E816a-h	S11	L6	M6
E817a-h	S11	L7	M6
E818a-h	S11	L8	M6
E819a-h	S11	L9	M6
E820a-h	S12	L1	M6

Example	S Group	L Group	M Group
E821a-h	S12	L2	M6
E822a-h	S12	L3	M6
E823a-h	S12	L4	M6
E824a-h	S12	L5	M6
E825a-h	S12	L6	M6
E826a-h	S12	L7	M6
E827a-h	S12	L8	M6
E828a-h	S12	L9	M6
E829a-h	S13	L1	M6
E830a-h	S13	L2	M6
E831a-h	S13	L3	M6
E832a-h	S13	L4	M6
E833a-h	S13	L5	M6
E834a-h	S13	L6	M6
E835a-h	S13	L7	M6
E836a-h	S13	L8	M6
E837a-h	S13	L9	M6
E838a-h	S14	L1	M6
E839a-h	S14	L2	M6
E840a-h	S14	L3	M6
E841a-h	S14	L4	M6
E842a-h	S14	L5	M6
E843a-h	S14	L6	M6
E844a-h	S14	L7	M6
E845a-h	S14	L8	M6
E846a-h	S14	L9	M6
E847a-h	S15	L1	M6
E848a-h	S15	L2	M6
E849a-h	S15	L3	M6
E850a-h	S15	L4	M6
E851a-h	S15	L5	M6
E852a-h	S15	L6	M6
E853a-h	S15	L7	M6
E854a-h	S15	L8	M6
E855a-h	S15	L9	M6
E856a-h	S16	L1	M6
E857a-h	S16	L2	M6
E858a-h	S16	L3	M6
E859a-h	S16	L4	M6
E860a-h	S16	L5	M6
E861a-h	S16	L6	M6
E862a-h	S16	L7	M6
E863a-h	S16	L8	M6
E864a-h	S16	L9	M6
E865a-h	S1	L1	M7
E866a-h	S1	L2	M7
E867a-h	S1	L3	M7

Example	S Group	L Group	M Group
E868a-h	S1	L4	M7
E869a-h	S1	L5	M7
E870a-h	S1	L6	M7
E871a-h	S1	L7	M7
E872a-h	S1	L8	M7
E873a-h	S1	L9	M7
E874a-h	S2	L1	M7
E875a-h	S2	L2	M7
E876a-h	S2	L3	M7
E877a-h	S2	L4	M7
E878a-h	S2	L5	M7
E879a-h	S2	L6	M7
E880a-h	S2	L7	M7
E881a-h	S2	L8	M7
E882a-h	S2	L9	M7
E883a-h	S3	L1	M7
E884a-h	S3	L2	M7
E885a-h	S3	L3	M7
E886a-h	S3	L4	M7
E887a-h	S3	L5	M7
E888a-h	S3	L6	M7
E889a-h	S3	L7	M7
E890a-h	S3	L8	M7
E891a-h	S3	L9	M7
E892a-h	S4	L1	M7
E893a-h	S4	L2	M7
E894a-h	S4	L3	M7
E895a-h	S4	L4	M7
E896a-h	S4	L5	M7
E897a-h	S4	L6	M7
E898a-h	S4	L7	M7
E899a-h	S4	L8	M7
E900a-h	S4	L9	M7
E901a-h	S5	L1	M7
E902a-h	S5	L2	M7
E903a-h	S5	L3	M7
E904a-h	S5	L4	M7
E905a-h	S5	L5	M7
E906a-h	S5	L6	M7
E907a-h	S5	L7	M7
E908a-h	S5	L8	M7
E909a-h	S5	L9	M7
E910a-h	S6	L1	M7
E911a-h	S6	L2	M7
E912a-h	S6	L3	M7
E913a-h	S6	L4	M7
E914a-h	S6	L5	M7

Example	S Group	L Group	M Group
E915a-h	S6	L6	M7
E916a-h	S6	L7	M7
E917a-h	S6	L8	M7
E918a-h	S6	L9	M7
E919a-h	S7	L1	M7
E920a-h	S7	L2	M7
E921a-h	S7	L3	M7
E922a-h	S7	L4	M7
E923a-h	S7	L5	M7
E924a-h	S7	L6	M7
E925a-h	S7	L7	M7
E926a-h	S7	L8	M7
E927a-h	S7	L9	M7
E928a-h	S8	L1	M7
E929a-h	S8	L2	M7
E930a-h	S8	L3	M7
E931a-h	S8	L4	M7
E932a-h	S8	L5	M7
E933a-h	S8	L6	M7
E934a-h	S8	L7	M7
E935a-h	S8	L8	M7
E936a-h	S8	L9	M7
E937a-h	S9	L1	M7
E938a-h	S9	L2	M7
E939a-h	S9	L3	M7
E940a-h	S9	L4	M7
E941a-h	S9	L5	M7
E942a-h	S9	L6	M7
E943a-h	S9	L7	M7
E944a-h	S9	L8	M7
E945a-h	S9	L9	M7
E946a-h	S10	L1	M7
E947a-h	S10	L2	M7
E948a-h	S10	L3	M7
E949a-h	S10	L4	M7
E950a-h	S10	L5	M7
E951a-h	S10	L6	M7
E952a-h	S10	L7	M7
E953a-h	S10	L8	M7
E954a-h	S10	L9	M7
E955a-h	S11	L1	M7
E956a-h	S11	L2	M7
E957a-h	S11	L3	M7
E958a-h	S11	L4	M7
E959a-h	S11	L5	M7
E960a-h	S11	L6	M7
E961a-h	S11	L7	M7

Example	S Group	L Group	M Group
E962a-h	S11	L8	M7
E963a-h	S11	L9	M7
E964a-h	S12	L1	M7
E965a-h	S12	L2	M7
E966a-h	S12	L3	M7
E967a-h	S12	L4	M7
E968a-h	S12	L5	M7
E969a-h	S12	L6	M7
E970a-h	S12	L7	M7
E971a-h	S12	L8	M7
E972a-h	S12	L9	M7
E973a-h	S13	L1	M7
E974a-h	S13	L2	M7
E975a-h	S13	L3	M7
E976a-h	S13	L4	M7
E977a-h	S13	L5	M7
E978a-h	S13	L6	M7
E979a-h	S13	L7	M7
E980a-h	S13	L8	M7
E981a-h	S13	L9	M7
E982a-h	S14	L1	M7
E983a-h	S14	L2	M7
E984a-h	S14	L3	M7
E985a-h	S14	L4	M7
E986a-h	S14	L5	M7
E987a-h	S14	L6	M7
E988a-h	S14	L7	M7
E989a-h	S14	L8	M7
E990a-h	S14	L9	M7
E991a-h	S15	L1	M7
E992a-h	S15	L2	M7
E993a-h	S15	L3	M7
E994a-h	S15	L4	M7
E995a-h	S15	L5	M7
E996a-h	S15	L6	M7
E997a-h	S15	L7	M7
E998a-h	S15	L8	M7
E999a-h	S15	L9	M7
E1000a-h	S16	L1	M7
E1001a-h	S16	L2	M7
E1002a-h	S16	L3	M7
E1003a-h	S16	L4	M7
E1004a-h	S16	L5	M7
E1005a-h	S16	L6	M7
E1006a-h	S16	L7	M7
E1007a-h	S16	L8	M7
E1008a-h	S16	L9	M7

Example	S Group	L Group	M Group
E1009a-h	S1	L1	M8
E1010a-h	S1	L2	M8
E1011a-h	S1	L3	M8
E1012a-h	S1	L4	M8
E1013a-h	S1	L5	M8
E1014a-h	S1	L6	M8
E1015a-h	S1	L7	M8
E1016a-h	S1	L8	M8
E1017a-h	S1	L9	M8
E1018a-h	S2	L1	M8
E1019a-h	S2	L2	M8
E1020a-h	S2	L3	M8
E1021a-h	S2	L4	M8
E1022a-h	S2	L5	M8
E1023a-h	S2	L6	M8
E1024a-h	S2	L7	M8
E1025a-h	S2	L8	M8
E1026a-h	S2	L9	M8
E1027a-h	S3	L1	M8
E1028a-h	S3	L2	M8
E1029a-h	S3	L3	M8
E1030a-h	S3	L4	M8
E1031a-h	S3	L5	M8
E1032a-h	S3	L6	M8
E1033a-h	S3	L7	M8
E1034a-h	S3	L8	M8
E1035a-h	S3	L9	M8
E1036a-h	S4	L1	M8
E1037a-h	S4	L2	M8
E1038a-h	S4	L3	M8
E1039a-h	S4	L4	M8
E1040a-h	S4	L5	M8
E1041a-h	S4	L6	M8
E1042a-h	S4	L7	M8
E1043a-h	S4	L8	M8
E1044a-h	S4	L9	M8
E1045a-h	S5	L1	M8
E1046a-h	S5	L2	M8
E1047a-h	S5	L3	M8
E1048a-h	S5	L4	M8
E1049a-h	S5	L5	M8
E1050a-h	S5	L6	M8
E1051a-h	S5	L7	M8
E1052a-h	S5	L8	M8
E1053a-h	S5	L9	M8
E1054a-h	S6	L1	M8
E1055a-h	S6	L2	M8

Example	S Group	L Group	M Group
E1056a-h	S6	L3	M8
E1057a-h	S6	L4	M8
E1058a-h	S6	L5	M8
E1059a-h	S6	L6	M8
E1060a-h	S6	L7	M8
E1061a-h	S6	L8	M8
E1062a-h	S6	L9	M8
E1063a-h	S7	L1	M8
E1064a-h	S7	L2	M8
E1065a-h	S7	L3	M8
E1066a-h	S7	L4	M8
E1067a-h	S7	L5	M8
E1068a-h	S7	L6	M8
E1069a-h	S7	L7	M8
E1070a-h	S7	L8	M8
E1071a-h	S7	L9	M8
E1072a-h	S8	L1	M8
E1073a-h	S8	L2	M8
E1074a-h	S8	L3	M8
E1075a-h	S8	L4	M8
E1076a-h	S8	L5	M8
E1077a-h	S8	L6	M8
E1078a-h	S8	L7	M8
E1079a-h	S8	L8	M8
E1080a-h	S8	L9	M8
E1081a-h	S9	L1	M8
E1082a-h	S9	L2	M8
E1083a-h	S9	L3	M8
E1084a-h	S9	L4	M8
E1085a-h	S9	L5	M8
E1086a-h	S9	L6	M8
E1087a-h	S9	L7	M8
E1088a-h	S9	L8	M8
E1089a-h	S9	L9	M8
E1090a-h	S10	L1	M8
E1091a-h	S10	L2	M8
E1092a-h	S10	L3	M8
E1093a-h	S10	L4	M8
E1094a-h	S10	L5	M8
E1095a-h	S10	L6	M8
E1096a-h	S10	L7	M8
E1097a-h	S10	L8	M8
E1098a-h	S10	L9	M8
E1099a-h	S11	L1	M8
E1100a-h	S11	L2	M8
E1101a-h	S11	L3	M8
E1102a-h	S11	L4	M8

Example	S Group	L Group	M Group
E1103a-h	S11	L5	M8
E1104a-h	S11	L6	M8
E1105a-h	S11	L7	M8
E1106a-h	S11	L8	M8
E1107a-h	S11	L9	M8
E1108a-h	S12	L1	M8
E1109a-h	S12	L2	M8
E1110a-h	S12	L3	M8
E1111a-h	S12	L4	M8
E1112a-h	S12	L5	M8
E1113a-h	S12	L6	M8
E1114a-h	S12	L7	M8
E1115a-h	S12	L8	M8
E1116a-h	S12	L9	M8
E1117a-h	S13	L1	M8
E1118a-h	S13	L2	M8
E1119a-h	S13	L3	M8
E1120a-h	S13	L4	M8
E1121a-h	S13	L5	M8
E1122a-h	S13	L6	M8
E1123a-h	S13	L7	M8
E1124a-h	S13	L8	M8
E1125a-h	S13	L9	M8
E1126a-h	S14	L1	M8
E1127a-h	S14	L2	M8
E1128a-h	S14	L3	M8
E1129a-h	S14	L4	M8
E1130a-h	S14	L5	M8
E1131a-h	S14	L6	M8
E1132a-h	S14	L7	M8
E1133a-h	S14	L8	M8
E1134a-h	S14	L9	M8
E1135a-h	S15	L1	M8
E1136a-h	S15	L2	M8
E1137a-h	S15	L3	M8
E1138a-h	S15	L4	M8
E1139a-h	S15	L5	M8
E1140a-h	S15	L6	M8
E1141a-h	S15	L7	M8
E1142a-h	S15	L8	M8
E1143a-h	S15	L9	M8
E1144a-h	S16	L1	M8
E1145a-h	S16	L2	M8
E1146a-h	S16	L3	M8
E1147a-h	S16	L4	M8
E1148a-h	S16	L5	M8
E1149a-h	S16	L6	M8

Example	S Group	L Group	M Group
E1150a-h	S16	L7	M8
E1151a-h	S16	L8	M8
E1152a-h	S16	L9	M8
E1153a-h	S1	L1	M9
E1154a-h	S1	L2	M9
E1155a-h	S1	L3	M9
E1156a-h	S1	L4	M9
E1157a-h	S1	L5	M9
E1158a-h	S1	L6	M9
E1159a-h	S1	L7	M9
E1160a-h	S1	L8	M9
E1161a-h	S1	L9	M9
E1162a-h	S2	L1	M9
E1163a-h	S2	L2	M9
E1164a-h	S2	L3	M9
E1165a-h	S2	L4	M9
E1166a-h	S2	L5	M9
E1167a-h	S2	L6	M9
E1168a-h	S2	L7	M9
E1169a-h	S2	L8	M9
E1170a-h	S2	L9	M9
E1171a-h	S3	L1	M9
E1172a-h	S3	L2	M9
E1173a-h	S3	L3	M9
E1174a-h	S3	L4	M9
E1175a-h	S3	L5	M9
E1176a-h	S3	L6	M9
E1177a-h	S3	L7	M9
E1178a-h	S3	L8	M9
E1179a-h	S3	L9	M9
E1180a-h	S4	L1	M9
E1181a-h	S4	L2	M9
E1182a-h	S4	L3	M9
E1183a-h	S4	L4	M9
E1184a-h	S4	L5	M9
E1185a-h	S4	L6	M9
E1186a-h	S4	L7	M9
E1187a-h	S4	L8	M9
E1188a-h	S4	L9	M9
E1189a-h	S5	L1	M9
E1190a-h	S5	L2	M9
E1191a-h	S5	L3	M9
E1192a-h	S5	L4	M9
E1193a-h	S5	L5	M9
E1194a-h	S5	L6	M9
E1195a-h	S5	L7	M9
E1196a-h	S5	L8	M9

Example	S Group	L Group	M Group
E1197a-h	S5	L9	M9
E1198a-h	S6	L1	M9
E1199a-h	S6	L2	M9
E1200a-h	S6	L3	M9
E1201a-h	S6	L4	M9
E1202a-h	S6	L5	M9
E1203a-h	S6	L6	M9
E1204a-h	S6	L7	M9
E1205a-h	S6	L8	M9
E1206a-h	S6	L9	M9
E1207a-h	S7	L1	M9
E1208a-h	S7	L2	M9
E1209a-h	S7	L3	M9
E1210a-h	S7	L4	M9
E1211a-h	S7	L5	M9
E1212a-h	S7	L6	M9
E1213a-h	S7	L7	M9
E1214a-h	S7	L8	M9
E1215a-h	S7	L9	M9
E1216a-h	S8	L1	M9
E1217a-h	S8	L2	M9
E1218a-h	S8	L3	M9
E1219a-h	S8	L4	M9
E1220a-h	S8	L5	M9
E1221a-h	S8	L6	M9
E1222a-h	S8	L7	M9
E1223a-h	S8	L8	M9
E1224a-h	S8	L9	M9
E1225a-h	S9	L1	M9
E1226a-h	S9	L2	M9
E1227a-h	S9	L3	M9
E1228a-h	S9	L4	M9
E1229a-h	S9	L5	M9
E1230a-h	S9	L6	M9
E1231a-h	S9	L7	M9
E1232a-h	S9	L8	M9
E1233a-h	S9	L9	M9
E1234a-h	S10	L1	M9
E1235a-h	S10	L2	M9
E1236a-h	S10	L3	M9
E1237a-h	S10	L4	M9
E1238a-h	S10	L5	M9
E1239a-h	S10	L6	M9
E1240a-h	S10	L7	M9
E1241a-h	S10	L8	M9
E1242a-h	S10	L9	M9
E1243a-h	S11	L1	M9

Example	S Group	L Group	M Group
E1244a-h	S11	L2	M9
E1245a-h	S11	L3	M9
E1246a-h	S11	L4	M9
E1247a-h	S11	L5	M9
E1248a-h	S11	L6	M9
E1249a-h	S11	L7	M9
E1250a-h	S11	L8	M9
E1251a-h	S11	L9	M9
E1252a-h	S12	L1	M9
E1253a-h	S12	L2	M9
E1254a-h	S12	L3	M9
E1255a-h	S12	L4	M9
E1256a-h	S12	L5	M9
E1257a-h	S12	L6	M9
E1258a-h	S12	L7	M9
E1259a-h	S12	L8	M9
E1260a-h	S12	L9	M9
E1261a-h	S13	L1	M9
E1262a-h	S13	L2	M9
E1263a-h	S13	L3	M9
E1264a-h	S13	L4	M9
E1265a-h	S13	L5	M9
E1266a-h	S13	L6	M9
E1267a-h	S13	L7	M9
E1268a-h	S13	L8	M9
E1269a-h	S13	L9	M9
E1270a-h	S14	L1	M9
E1271a-h	S14	L2	M9
E1272a-h	S14	L3	M9
E1273a-h	S14	L4	M9
E1274a-h	S14	L5	M9
E1275a-h	S14	L6	M9
E1276a-h	S14	L7	M9
E1277a-h	S14	L8	M9
E1278a-h	S14	L9	M9
E1279a-h	S15	L1	M9
E1280a-h	S15	L2	M9
E1281a-h	S15	L3	M9
E1282a-h	S15	L4	M9
E1283a-h	S15	L5	M9
E1284a-h	S15	L6	M9
E1285a-h	S15	L7	M9
E1286a-h	S15	L8	M9
E1287a-h	S15	L9	M9
E1288a-h	S16	L1	M9
E1289a-h	S16	L2	M9
E1290a-h	S16	L3	M9

Example	S Group	L Group	M Group
E1291a-h	S16	L4	M9
E1292a-h	S16	L5	M9
E1293a-h	S16	L6	M9
E1294a-h	S16	L7	M9
E1295a-h	S16	L8	M9
E1296a-h	S16	L9	M9
E1297a-h	S1	L1	M10
E1298a-h	S1	L2	M10
E1299a-h	S1	L3	M10
E1300a-h	S1	L4	M10
E1301a-h	S1	L5	M10
E1302a-h	S1	L6	M10
E1303a-h	S1	L7	M10
E1304a-h	S1	L8	M10
E1305a-h	S1	L9	M10
E1306a-h	S2	L1	M10
E1307a-h	S2	L2	M10
E1308a-h	S2	L3	M10
E1309a-h	S2	L4	M10
E1310a-h	S2	L5	M10
E1311a-h	S2	L6	M10
E1312a-h	S2	L7	M10
E1313a-h	S2	L8	M10
E1314a-h	S2	L9	M10
E1315a-h	S3	L1	M10
E1316a-h	S3	L2	M10
E1317a-h	S3	L3	M10
E1318a-h	S3	L4	M10
E1319a-h	S3	L5	M10
E1320a-h	S3	L6	M10
E1321a-h	S3	L7	M10
E1322a-h	S3	L8	M10
E1323a-h	S3	L9	M10
E1324a-h	S4	L1	M10
E1325a-h	S4	L2	M10
E1326a-h	S4	L3	M10
E1327a-h	S4	L4	M10
E1328a-h	S4	L5	M10
E1329a-h	S4	L6	M10
E1330a-h	S4	L7	M10
E1331a-h	S4	L8	M10
E1332a-h	S4	L9	M10
E1333a-h	S5	L1	M10
E1334a-h	S5	L2	M10
E1335a-h	S5	L3	M10
E1336a-h	S5	L4	M10
E1337a-h	S5	L5	M10

Example	S Group	L Group	M Group
E1338a-h	S5	L6	M10
E1339a-h	S5	L7	M10
E1340a-h	S5	L8	M10
E1341a-h	S5	L9	M10
E1342a-h	S6	L1	M10
E1343a-h	S6	L2	M10
E1344a-h	S6	L3	M10
E1345a-h	S6	L4	M10
E1346a-h	S6	L5	M10
E1347a-h	S6	L6	M10
E1348a-h	S6	L7	M10
E1349a-h	S6	L8	M10
E1350a-h	S6	L9	M10
E1351a-h	S7	L1	M10
E1352a-h	S7	L2	M10
E1353a-h	S7	L3	M10
E1354a-h	S7	L4	M10
E1355a-h	S7	L5	M10
E1356a-h	S7	L6	M10
E1357a-h	S7	L7	M10
E1358a-h	S7	L8	M10
E1359a-h	S7	L9	M10
E1360a-h	S8	L1	M10
E1361a-h	S8	L2	M10
E1362a-h	S8	L3	M10
E1363a-h	S8	L4	M10
E1364a-h	S8	L5	M10
E1365a-h	S8	L6	M10
E1366a-h	S8	L7	M10
E1367a-h	S8	L8	M10
E1368a-h	S8	L9	M10
E1369a-h	S9	L1	M10
E1370a-h	S9	L2	M10
E1371a-h	S9	L3	M10
E1372a-h	S9	L4	M10
E1373a-h	S9	L5	M10
E1374a-h	S9	L6	M10
E1375a-h	S9	L7	M10
E1376a-h	S9	L8	M10
E1377a-h	S9	L9	M10
E1378a-h	S10	L1	M10
E1379a-h	S10	L2	M10
E1380a-h	S10	L3	M10
E1381a-h	S10	L4	M10
E1382a-h	S10	L5	M10
E1383a-h	S10	L6	M10
E1384a-h	S10	L7	M10

Example	S Group	L Group	M Group
E1385a-h	S10	L8	M10
E1386a-h	S10	L9	M10
E1387a-h	S11	L1	M10
E1388a-h	S11	L2	M10
E1389a-h	S11	L3	M10
E1390a-h	S11	L4	M10
E1391a-h	S11	L5	M10
E1392a-h	S11	L6	M10
E1393a-h	S11	L7	M10
E1394a-h	S11	L8	M10
E1395a-h	S11	L9	M10
E1396a-h	S12	L1	M10
E1397a-h	S12	L2	M10
E1398a-h	S12	L3	M10
E1399a-h	S12	L4	M10
E1400a-h	S12	L5	M10
E1401a-h	S12	L6	M10
E1402a-h	S12	L7	M10
E1403a-h	S12	L8	M10
E1404a-h	S12	L9	M10
E1405a-h	S13	L1	M10
E1406a-h	S13	L2	M10
E1407a-h	S13	L3	M10
E1408a-h	S13	L4	M10
E1409a-h	S13	L5	M10
E1410a-h	S13	L6	M10
E1411a-h	S13	L7	M10
E1412a-h	S13	L8	M10
E1413a-h	S13	L9	M10
E1414a-h	S14	L1	M10
E1415a-h	S14	L2	M10
E1416a-h	S14	L3	M10
E1417a-h	S14	L4	M10
E1418a-h	S14	L5	M10
E1419a-h	S14	L6	M10
E1420a-h	S14	L7	M10
E1421a-h	S14	L8	M10
E1422a-h	S14	L9	M10
E1423a-h	S15	L1	M10
E1424a-h	S15	L2	M10
E1425a-h	S15	L3	M10
E1426a-h	S15	L4	M10
E1427a-h	S15	L5	M10
E1428a-h	S15	L6	M10
E1429a-h	S15	L7	M10
E1430a-h	S15	L8	M10
E1431a-h	S15	L9	M10

Example	S Group	L Group	M Group
E1432a-h	S16	L1	M10
E1433a-h	S16	L2	M10
E1434a-h	S16	L3	M10
E1435a-h	S16	L4	M10
E1436a-h	S16	L5	M10
E1437a-h	S16	L6	M10
E1438a-h	S16	L7	M10
E1439a-h	S16	L8	M10
E1440a-h	S16	L9	M10
E1441a-h	S1	L1	M11
E1442a-h	S1	L2	M11
E1443a-h	S1	L3	M11
E1444a-h	S1	L4	M11
E1445a-h	S1	L5	M11
E1446a-h	S1	L6	M11
E1447a-h	S1	L7	M11
E1448a-h	S1	L8	M11
E1449a-h	S1	L9	M11
E1450a-h	S2	L1	M11
E1451a-h	S2	L2	M11
E1452a-h	S2	L3	M11
E1453a-h	S2	L4	M11
E1454a-h	S2	L5	M11
E1455a-h	S2	L6	M11
E1456a-h	S2	L7	M11
E1457a-h	S2	L8	M11
E1458a-h	S2	L9	M11
E1459a-h	S3	L1	M11
E1460a-h	S3	L2	M11
E1461a-h	S3	L3	M11
E1462a-h	S3	L4	M11
E1463a-h	S3	L5	M11
E1464a-h	S3	L6	M11
E1465a-h	S3	L7	M11
E1466a-h	S3	L8	M11
E1467a-h	S3	L9	M11
E1468a-h	S4	L1	M11
E1469a-h	S4	L2	M11
E1470a-h	S4	L3	M11
E1471a-h	S4	L4	M11
E1472a-h	S4	L5	M11
E1473a-h	S4	L6	M11
E1474a-h	S4	L7	M11
E1475a-h	S4	L8	M11
E1476a-h	S4	L9	M11
E1477a-h	S5	L1	M11
E1478a-h	S5	L2	M11

Example	S Group	L Group	M Group
E1479a-h	S5	L3	M11
E1480a-h	S5	L4	M11
E1481a-h	S5	L5	M11
E1482a-h	S5	L6	M11
E1483a-h	S5	L7	M11
E1484a-h	S5	L8	M11
E1485a-h	S5	L9	M11
E1486a-h	S6	L1	M11
E1487a-h	S6	L2	M11
E1488a-h	S6	L3	M11
E1489a-h	S6	L4	M11
E1490a-h	S6	L5	M11
E1491a-h	S6	L6	M11
E1492a-h	S6	L7	M11
E1493a-h	S6	L8	M11
E1494a-h	S6	L9	M11
E1495a-h	S7	L1	M11
E1496a-h	S7	L2	M11
E1497a-h	S7	L3	M11
E1498a-h	S7	L4	M11
E1499a-h	S7	L5	M11
E1500a-h	S7	L6	M11
E1501a-h	S7	L7	M11
E1502a-h	S7	L8	M11
E1503a-h	S7	L9	M11
E1504a-h	S8	L1	M11
E1505a-h	S8	L2	M11
E1506a-h	S8	L3	M11
E1507a-h	S8	L4	M11
E1508a-h	S8	L5	M11
E1509a-h	S8	L6	M11
E1510a-h	S8	L7	M11
E1511a-h	S8	L8	M11
E1512a-h	S8	L9	M11
E1513a-h	S9	L1	M11
E1514a-h	S9	L2	M11
E1515a-h	S9	L3	M11
E1516a-h	S9	L4	M11
E1517a-h	S9	L5	M11
E1518a-h	S9	L6	M11
E1519a-h	S9	L7	M11
E1520a-h	S9	L8	M11
E1521a-h	S9	L9	M11
E1522a-h	S10	L1	M11
E1523a-h	S10	L2	M11
E1524a-h	S10	L3	M11
E1525a-h	S10	L4	M11

Example	S Group	L Group	M Group
E1526a-h	S10	L5	M11
E1527a-h	S10	L6	M11
E1528a-h	S10	L7	M11
E1529a-h	S10	L8	M11
E1530a-h	S10	L9	M11
E1531a-h	S11	L1	M11
E1532a-h	S11	L2	M11
E1533a-h	S11	L3	M11
E1534a-h	S11	L4	M11
E1535a-h	S11	L5	M11
E1536a-h	S11	L6	M11
E1537a-h	S11	L7	M11
E1538a-h	S11	L8	M11
E1539a-h	S11	L9	M11
E1540a-h	S12	L1	M11
E1541a-h	S12	L2	M11
E1542a-h	S12	L3	M11
E1543a-h	S12	L4	M11
E1544a-h	S12	L5	M11
E1545a-h	S12	L6	M11
E1546a-h	S12	L7	M11
E1547a-h	S12	L8	M11
E1548a-h	S12	L9	M11
E1549a-h	S13	L1	M11
E1550a-h	S13	L2	M11
E1551a-h	S13	L3	M11
E1552a-h	S13	L4	M11
E1553a-h	S13	L5	M11
E1554a-h	S13	L6	M11
E1555a-h	S13	L7	M11
E1556a-h	S13	L8	M11
E1557a-h	S13	L9	M11
E1558a-h	S14	L1	M11
E1559a-h	S14	L2	M11
E1560a-h	S14	L3	M11
E1561a-h	S14	L4	M11
E1562a-h	S14	L5	M11
E1563a-h	S14	L6	M11
E1564a-h	S14	L7	M11
E1565a-h	S14	L8	M11
E1566a-h	S14	L9	M11
E1567a-h	S15	L1	M11
E1568a-h	S15	L2	M11
E1569a-h	S15	L3	M11
E1570a-h	S15	L4	M11
E1571a-h	S15	L5	M11
E1572a-h	S15	L6	M11

Example	S Group	L Group	M Group
E1573a-h	S15	L7	M11
E1574a-h	S15	L8	M11
E1575a-h	S15	L9	M11
E1576a-h	S16	L1	M11
E1577a-h	S16	L2	M11
E1578a-h	S16	L3	M11
E1579a-h	S16	L4	M11
E1580a-h	S16	L5	M11
E1581a-h	S16	L6	M11
E1582a-h	S16	L7	M11
E1583a-h	S16	L8	M11
E1584a-h	S16	L9	M11
E1585a-h	S1	L1	M12
E1586a-h	S1	L2	M12
E1587a-h	S1	L3	M12
E1588a-h	S1	L4	M12
E1589a-h	S1	L5	M12
E1590a-h	S1	L6	M12
E1591a-h	S1	L7	M12
E1592a-h	S1	L8	M12
E1593a-h	S1	L9	M12
E1594a-h	S2	L1	M12
E1595a-h	S2	L2	M12
E1596a-h	S2	L3	M12
E1597a-h	S2	L4	M12
E1598a-h	S2	L5	M12
E1599a-h	S2	L6	M12
E1600a-h	S2	L7	M12
E1601a-h	S2	L8	M12
E1602a-h	S2	L9	M12
E1603a-h	S3	L1	M12
E1604a-h	S3	L2	M12
E1605a-h	S3	L3	M12
E1606a-h	S3	L4	M12
E1607a-h	S3	L5	M12
E1608a-h	S3	L6	M12
E1609a-h	S3	L7	M12
E1610a-h	S3	L8	M12
E1611a-h	S3	L9	M12
E1612a-h	S4	L1	M12
E1613a-h	S4	L2	M12
E1614a-h	S4	L3	M12
E1615a-h	S4	L4	M12
E1616a-h	S4	L5	M12
E1617a-h	S4	L6	M12
E1618a-h	S4	L7	M12
E1619a-h	S4	L8	M12

Example	S Group	L Group	M Group
E1620a-h	S4	L9	M12
E1621a-h	S5	L1	M12
E1622a-h	S5	L2	M12
E1623a-h	S5	L3	M12
E1624a-h	S5	L4	M12
E1625a-h	S5	L5	M12
E1626a-h	S5	L6	M12
E1627a-h	S5	L7	M12
E1628a-h	S5	L8	M12
E1629a-h	S5	L9	M12
E1630a-h	S6	L1	M12
E1631a-h	S6	L2	M12
E1632a-h	S6	L3	M12
E1633a-h	S6	L4	M12
E1634a-h	S6	L5	M12
E1635a-h	S6	L6	M12
E1636a-h	S6	L7	M12
E1637a-h	S6	L8	M12
E1638a-h	S6	L9	M12
E1639a-h	S7	L1	M12
E1640a-h	S7	L2	M12
E1641a-h	S7	L3	M12
E1642a-h	S7	L4	M12
E1643a-h	S7	L5	M12
E1644a-h	S7	L6	M12
E1645a-h	S7	L7	M12
E1646a-h	S7	L8	M12
E1647a-h	S7	L9	M12
E1648a-h	S8	L1	M12
E1649a-h	S8	L2	M12
E1650a-h	S8	L3	M12
E1651a-h	S8	L4	M12
E1652a-h	S8	L5	M12
E1653a-h	S8	L6	M12
E1654a-h	S8	L7	M12
E1655a-h	S8	L8	M12
E1656a-h	S8	L9	M12
E1657a-h	S9	L1	M12
E1658a-h	S9	L2	M12
E1659a-h	S9	L3	M12
E1660a-h	S9	L4	M12
E1661a-h	S9	L5	M12
E1662a-h	S9	L6	M12
E1663a-h	S9	L7	M12
E1664a-h	S9	L8	M12
E1665a-h	S9	L9	M12
E1666a-h	S10	L1	M12

Example	S Group	L Group	M Group
E1667a-h	S10	L2	M12
E1668a-h	S10	L3	M12
E1669a-h	S10	L4	M12
E1670a-h	S10	L5	M12
E1671a-h	S10	L6	M12
E1672a-h	S10	L7	M12
E1673a-h	S10	L8	M12
E1674a-h	S10	L9	M12
E1675a-h	S11	L1	M12
E1676a-h	S11	L2	M12
E1677a-h	S11	L3	M12
E1678a-h	S11	L4	M12
E1679a-h	S11	L5	M12
E1680a-h	S11	L6	M12
E1681a-h	S11	L7	M12
E1682a-h	S11	L8	M12
E1683a-h	S11	L9	M12
E1684a-h	S12	L1	M12
E1685a-h	S12	L2	M12
E1686a-h	S12	L3	M12
E1687a-h	S12	L4	M12
E1688a-h	S12	L5	M12
E1689a-h	S12	L6	M12
E1690a-h	S12	L7	M12
E1691a-h	S12	L8	M12
E1692a-h	S12	L9	M12
E1693a-h	S13	L1	M12
E1694a-h	S13	L2	M12
E1695a-h	S13	L3	M12
E1696a-h	S13	L4	M12
E1697a-h	S13	L5	M12
E1698a-h	S13	L6	M12
E1699a-h	S13	L7	M12
E1700a-h	S13	L8	M12
E1701a-h	S13	L9	M12
E1702a-h	S14	L1	M12
E1703a-h	S14	L2	M12
E1704a-h	S14	L3	M12
E1705a-h	S14	L4	M12
E1706a-h	S14	L5	M12
E1707a-h	S14	L6	M12
E1708a-h	S14	L7	M12
E1709a-h	S14	L8	M12
E1710a-h	S14	L9	M12
E1711a-h	S15	L1	M12
E1712a-h	S15	L2	M12
E1713a-h	S15	L3	M12

Example	S Group	L Group	M Group
E1714a-h	S15	L4	M12
E1715a-h	S15	L5	M12
E1716a-h	S15	L6	M12
E1717a-h	S15	L7	M12
E1718a-h	S15	L8	M12
E1719a-h	S15	L9	M12
E1720a-h	S16	L1	M12
E1721a-h	S16	L2	M12
E1722a-h	S16	L3	M12
E1723a-h	S16	L4	M12
E1724a-h	S16	L5	M12
E1725a-h	S16	L6	M12
E1726a-h	S16	L7	M12
E1727a-h	S16	L8	M12
E1728a-h	S16	L9	M12
E1729a-h	S1	L1	M13
E1730a-h	S1	L2	M13
E1731a-h	S1	L3	M13
E1732a-h	S1	L4	M13
E1733a-h	S1	L5	M13
E1734a-h	S1	L6	M13
E1735a-h	S1	L7	M13
E1736a-h	S1	L8	M13
E1737a-h	S1	L9	M13
E1738a-h	S2	L1	M13
E1739a-h	S2	L2	M13
E1740a-h	S2	L3	M13
E1741a-h	S2	L4	M13
E1742a-h	S2	L5	M13
E1743a-h	S2	L6	M13
E1744a-h	S2	L7	M13
E1745a-h	S2	L8	M13
E1746a-h	S2	L9	M13
E1747a-h	S3	L1	M13
E1748a-h	S3	L2	M13
E1749a-h	S3	L3	M13
E1750a-h	S3	L4	M13
E1751a-h	S3	L5	M13
E1752a-h	S3	L6	M13
E1753a-h	S3	L7	M13
E1754a-h	S3	L8	M13
E1755a-h	S3	L9	M13
E1756a-h	S4	L1	M13
E1757a-h	S4	L2	M13
E1758a-h	S4	L3	M13
E1759a-h	S4	L4	M13
E1760a-h	S4	L5	M13

Example	S Group	L Group	M Group
E1761a-h	S4	L6	M13
E1762a-h	S4	L7	M13
E1763a-h	S4	L8	M13
E1764a-h	S4	L9	M13
E1765a-h	S5	L1	M13
E1766a-h	S5	L2	M13
E1767a-h	S5	L3	M13
E1768a-h	S5	L4	M13
E1769a-h	S5	L5	M13
E1770a-h	S5	L6	M13
E1771a-h	S5	L7	M13
E1772a-h	S5	L8	M13
E1773a-h	S5	L9	M13
E1774a-h	S6	L1	M13
E1775a-h	S6	L2	M13
E1776a-h	S6	L3	M13
E1777a-h	S6	L4	M13
E1778a-h	S6	L5	M13
E1779a-h	S6	L6	M13
E1780a-h	S6	L7	M13
E1781a-h	S6	L8	M13
E1782a-h	S6	L9	M13
E1783a-h	S7	L1	M13
E1784a-h	S7	L2	M13
E1785a-h	S7	L3	M13
E1786a-h	S7	L4	M13
E1787a-h	S7	L5	M13
E1788a-h	S7	L6	M13
E1789a-h	S7	L7	M13
E1790a-h	S7	L8	M13
E1791a-h	S7	L9	M13
E1792a-h	S8	L1	M13
E1793a-h	S8	L2	M13
E1794a-h	S8	L3	M13
E1795a-h	S8	L4	M13
E1796a-h	S8	L5	M13
E1797a-h	S8	L6	M13
E1798a-h	S8	L7	M13
E1799a-h	S8	L8	M13
E1800a-h	S8	L9	M13
E1801a-h	S9	L1	M13
E1802a-h	S9	L2	M13
E1803a-h	S9	L3	M13
E1804a-h	S9	L4	M13
E1805a-h	S9	L5	M13
E1806a-h	S9	L6	M13
E1807a-h	S9	L7	M13

Example	S Group	L Group	M Group
E1808a-h	S9	L8	M13
E1809a-h	S9	L9	M13
E1810a-h	S10	L1	M13
E1811a-h	S10	L2	M13
E1812a-h	S10	L3	M13
E1813a-h	S10	L4	M13
E1814a-h	S10	L5	M13
E1815a-h	S10	L6	M13
E1816a-h	S10	L7	M13
E1817a-h	S10	L8	M13
E1818a-h	S10	L9	M13
E1819a-h	S11	L1	M13
E1820a-h	S11	L2	M13
E1821a-h	S11	L3	M13
E1822a-h	S11	L4	M13
E1823a-h	S11	L5	M13
E1824a-h	S11	L6	M13
E1825a-h	S11	L7	M13
E1826a-h	S11	L8	M13
E1827a-h	S11	L9	M13
E1828a-h	S12	L1	M13
E1829a-h	S12	L2	M13
E1830a-h	S12	L3	M13
E1831a-h	S12	L4	M13
E1832a-h	S12	L5	M13
E1833a-h	S12	L6	M13
E1834a-h	S12	L7	M13
E1835a-h	S12	L8	M13
E1836a-h	S12	L9	M13
E1837a-h	S13	L1	M13
E1838a-h	S13	L2	M13
E1839a-h	S13	L3	M13
E1840a-h	S13	L4	M13
E1841a-h	S13	L5	M13
E1842a-h	S13	L6	M13
E1843a-h	S13	L7	M13
E1844a-h	S13	L8	M13
E1845a-h	S13	L9	M13
E1846a-h	S14	L1	M13
E1847a-h	S14	L2	M13
E1848a-h	S14	L3	M13
E1849a-h	S14	L4	M13
E1850a-h	S14	L5	M13
E1851a-h	S14	L6	M13
E1852a-h	S14	L7	M13
E1853a-h	S14	L8	M13
E1854a-h	S14	L9	M13

Example	S Group	L Group	M Group
E1855a-h	S15	L1	M13
E1856a-h	S15	L2	M13
E1857a-h	S15	L3	M13
E1858a-h	S15	L4	M13
E1859a-h	S15	L5	M13
E1860a-h	S15	L6	M13
E1861a-h	S15	L7	M13
E1862a-h	S15	L8	M13
E1863a-h	S15	L9	M13
E1864a-h	S16	L1	M13
E1865a-h	S16	L2	M13
E1866a-h	S16	L3	M13
E1867a-h	S16	L4	M13
E1868a-h	S16	L5	M13
E1869a-h	S16	L6	M13
E1870a-h	S16	L7	M13
E1871a-h	S16	L8	M13
E1872a-h	S16	L9	M13
E1873a-h	S1	L1	M14
E1874a-h	S1	L2	M14
E1875a-h	S1	L3	M14
E1876a-h	S1	L4	M14
E1877a-h	S1	L5	M14
E1878a-h	S1	L6	M14
E1879a-h	S1	L7	M14
E1880a-h	S1	L8	M14
E1881a-h	S1	L9	M14
E1882a-h	S2	L1	M14
E1883a-h	S2	L2	M14
E1884a-h	S2	L3	M14
E1885a-h	S2	L4	M14
E1886a-h	S2	L5	M14
E1887a-h	S2	L6	M14
E1888a-h	S2	L7	M14
E1889a-h	S2	L8	M14
E1890a-h	S2	L9	M14
E1891a-h	S3	L1	M14
E1892a-h	S3	L2	M14
E1893a-h	S3	L3	M14
E1894a-h	S3	L4	M14
E1895a-h	S3	L5	M14
E1896a-h	S3	L6	M14
E1897a-h	S3	L7	M14
E1898a-h	S3	L8	M14
E1899a-h	S3	L9	M14
E1900a-h	S4	L1	M14
E1901a-h	S4	L2	M14

Example	S Group	L Group	M Group
E1902a-h	S4	L3	M14
E1903a-h	S4	L4	M14
E1904a-h	S4	L5	M14
E1905a-h	S4	L6	M14
E1906a-h	S4	L7	M14
E1907a-h	S4	L8	M14
E1908a-h	S4	L9	M14
E1909a-h	S5	L1	M14
E1910a-h	S5	L2	M14
E1911a-h	S5	L3	M14
E1912a-h	S5	L4	M14
E1913a-h	S5	L5	M14
E1914a-h	S5	L6	M14
E1915a-h	S5	L7	M14
E1916a-h	S5	L8	M14
E1917a-h	S5	L9	M14
E1918a-h	S6	L1	M14
E1919a-h	S6	L2	M14
E1920a-h	S6	L3	M14
E1921a-h	S6	L4	M14
E1922a-h	S6	L5	M14
E1923a-h	S6	L6	M14
E1924a-h	S6	L7	M14
E1925a-h	S6	L8	M14
E1926a-h	S6	L9	M14
E1927a-h	S7	L1	M14
E1928a-h	S7	L2	M14
E1929a-h	S7	L3	M14
E1930a-h	S7	L4	M14
E1931a-h	S7	L5	M14
E1932a-h	S7	L6	M14
E1933a-h	S7	L7	M14
E1934a-h	S7	L8	M14
E1935a-h	S7	L9	M14
E1936a-h	S8	L1	M14
E1937a-h	S8	L2	M14
E1938a-h	S8	L3	M14
E1939a-h	S8	L4	M14
E1940a-h	S8	L5	M14
E1941a-h	S8	L6	M14
E1942a-h	S8	L7	M14
E1943a-h	S8	L8	M14
E1944a-h	S8	L9	M14
E1945a-h	S9	L1	M14
E1946a-h	S9	L2	M14
E1947a-h	S9	L3	M14
E1948a-h	S9	L4	M14

Example	S Group	L Group	M Group
E1949a-h	S9	L5	M14
E1950a-h	S9	L6	M14
E1951a-h	S9	L7	M14
E1952a-h	S9	L8	M14
E1953a-h	S9	L9	M14
E1954a-h	S10	L1	M14
E1955a-h	S10	L2	M14
E1956a-h	S10	L3	M14
E1957a-h	S10	L4	M14
E1958a-h	S10	L5	M14
E1959a-h	S10	L6	M14
E1960a-h	S10	L7	M14
E1961a-h	S10	L8	M14
E1962a-h	S10	L9	M14
E1963a-h	S11	L1	M14
E1964a-h	S11	L2	M14
E1965a-h	S11	L3	M14
E1966a-h	S11	L4	M14
E1967a-h	S11	L5	M14
E1968a-h	S11	L6	M14
E1969a-h	S11	L7	M14
E1970a-h	S11	L8	M14
E1971a-h	S11	L9	M14
E1972a-h	S12	L1	M14
E1973a-h	S12	L2	M14
E1974a-h	S12	L3	M14
E1975a-h	S12	L4	M14
E1976a-h	S12	L5	M14
E1977a-h	S12	L6	M14
E1978a-h	S12	L7	M14
E1979a-h	S12	L8	M14
E1980a-h	S12	L9	M14
E1981a-h	S13	L1	M14
E1982a-h	S13	L2	M14
E1983a-h	S13	L3	M14
E1984a-h	S13	L4	M14
E1985a-h	S13	L5	M14
E1986a-h	S13	L6	M14
E1987a-h	S13	L7	M14
E1988a-h	S13	L8	M14
E1989a-h	S13	L9	M14
E1990a-h	S14	L1	M14
E1991a-h	S14	L2	M14
E1992a-h	S14	L3	M14
E1993a-h	S14	L4	M14
E1994a-h	S14	L5	M14
E1995a-h	S14	L6	M14

Example	S Group	L Group	M Group
E1996a-h	S14	L7	M14
E1997a-h	S14	L8	M14
E1998a-h	S14	L9	M14
E1999a-h	S15	L1	M14
E2000a-h	S15	L2	M14
E2001a-h	S15	L3	M14
E2002a-h	S15	L4	M14
E2003a-h	S15	L5	M14
E2004a-h	S15	L6	M14
E2005a-h	S15	L7	M14
E2006a-h	S15	L8	M14
E2007a-h	S15	L9	M14
E2008a-h	S16	L1	M14
E2009a-h	S16	L2	M14
E2010a-h	S16	L3	M14
E2011a-h	S16	L4	M14
E2012a-h	S16	L5	M14
E2013a-h	S16	L6	M14
E2014a-h	S16	L7	M14
E2015a-h	S16	L8	M14
E2016a-h	S16	L9	M14
E2017a-h	S1	L1	M15
E2018a-h	S1	L2	M15
E2019a-h	S1	L3	M15
E2020a-h	S1	L4	M15
E2021a-h	S1	L5	M15
E2022a-h	S1	L6	M15
E2023a-h	S1	L7	M15
E2024a-h	S1	L8	M15
E2025a-h	S1	L9	M15
E2026a-h	S2	L1	M15
E2027a-h	S2	L2	M15
E2028a-h	S2	L3	M15
E2029a-h	S2	L4	M15
E2030a-h	S2	L5	M15
E2031a-h	S2	L6	M15
E2032a-h	S2	L7	M15
E2033a-h	S2	L8	M15
E2034a-h	S2	L9	M15
E2035a-h	S3	L1	M15
E2036a-h	S3	L2	M15
E2037a-h	S3	L3	M15
E2038a-h	S3	L4	M15
E2039a-h	S3	L5	M15
E2040a-h	S3	L6	M15
E2041a-h	S3	L7	M15
E2042a-h	S3	L8	M15

Example	S Group	L Group	M Group
E2043a-h	S3	L9	M15
E2044a-h	S4	L1	M15
E2045a-h	S4	L2	M15
E2046a-h	S4	L3	M15
E2047a-h	S4	L4	M15
E2048a-h	S4	L5	M15
E2049a-h	S4	L6	M15
E2050a-h	S4	L7	M15
E2051a-h	S4	L8	M15
E2052a-h	S4	L9	M15
E2053a-h	S5	L1	M15
E2054a-h	S5	L2	M15
E2055a-h	S5	L3	M15
E2056a-h	S5	L4	M15
E2057a-h	S5	L5	M15
E2058a-h	S5	L6	M15
E2059a-h	S5	L7	M15
E2060a-h	S5	L8	M15
E2061a-h	S5	L9	M15
E2062a-h	S6	L1	M15
E2063a-h	S6	L2	M15
E2064a-h	S6	L3	M15
E2065a-h	S6	L4	M15
E2066a-h	S6	L5	M15
E2067a-h	S6	L6	M15
E2068a-h	S6	L7	M15
E2069a-h	S6	L8	M15
E2070a-h	S6	L9	M15
E2071a-h	S7	L1	M15
E2072a-h	S7	L2	M15
E2073a-h	S7	L3	M15
E2074a-h	S7	L4	M15
E2075a-h	S7	L5	M15
E2076a-h	S7	L6	M15
E2077a-h	S7	L7	M15
E2078a-h	S7	L8	M15
E2079a-h	S7	L9	M15
E2080a-h	S8	L1	M15
E2081a-h	S8	L2	M15
E2082a-h	S8	L3	M15
E2083a-h	S8	L4	M15
E2084a-h	S8	L5	M15
E2085a-h	S8	L6	M15
E2086a-h	S8	L7	M15
E2087a-h	S8	L8	M15
E2088a-h	S8	L9	M15
E2089a-h	S9	L1	M15

Example	S Group	L Group	M Group
E2090a-h	S9	L2	M15
E2091a-h	S9	L3	M15
E2092a-h	S9	L4	M15
E2093a-h	S9	L5	M15
E2094a-h	S9	L6	M15
E2095a-h	S9	L7	M15
E2096a-h	S9	L8	M15
E2097a-h	S9	L9	M15
E2098a-h	S10	L1	M15
E2099a-h	S10	L2	M15
E2100a-h	S10	L3	M15
E2101a-h	S10	L4	M15
E2102a-h	S10	L5	M15
E2103a-h	S10	L6	M15
E2104a-h	S10	L7	M15
E2105a-h	S10	L8	M15
E2106a-h	S10	L9	M15
E2107a-h	S11	L1	M15
E2108a-h	S11	L2	M15
E2109a-h	S11	L3	M15
E2110a-h	S11	L4	M15
E2111a-h	S11	L5	M15
E2112a-h	S11	L6	M15
E2113a-h	S11	L7	M15
E2114a-h	S11	L8	M15
E2115a-h	S11	L9	M15
E2116a-h	S12	L1	M15
E2117a-h	S12	L2	M15
E2118a-h	S12	L3	M15
E2119a-h	S12	L4	M15
E2120a-h	S12	L5	M15
E2121a-h	S12	L6	M15
E2122a-h	S12	L7	M15
E2123a-h	S12	L8	M15
E2124a-h	S12	L9	M15
E2125a-h	S13	L1	M15
E2126a-h	S13	L2	M15
E2127a-h	S13	L3	M15
E2128a-h	S13	L4	M15
E2129a-h	S13	L5	M15
E2130a-h	S13	L6	M15
E2131a-h	S13	L7	M15
E2132a-h	S13	L8	M15
E2133a-h	S13	L9	M15
E2134a-h	S14	L1	M15
E2135a-h	S14	L2	M15
E2136a-h	S14	L3	M15

Example	S Group	L Group	M Group
E2137a-h	S14	L4	M15
E2138a-h	S14	L5	M15
E2139a-h	S14	L6	M15
E2140a-h	S14	L7	M15
E2141a-h	S14	L8	M15
E2142a-h	S14	L9	M15
E2143a-h	S15	L1	M15
E2144a-h	S15	L2	M15
E2145a-h	S15	L3	M15
E2146a-h	S15	L4	M15
E2147a-h	S15	L5	M15
E2148a-h	S15	L6	M15
E2149a-h	S15	L7	M15
E2150a-h	S15	L8	M15
E2151a-h	S15	L9	M15
E2152a-h	S16	L1	M15
E2153a-h	S16	L2	M15
E2154a-h	S16	L3	M15
E2155a-h	S16	L4	M15
E2156a-h	S16	L5	M15
E2157a-h	S16	L6	M15
E2158a-h	S16	L7	M15
E2159a-h	S16	L8	M15
E2160a-h	S16	L9	M15
E2161a-h	S1	L1	M16
E2162a-h	S1	L2	M16
E2163a-h	S1	L3	M16
E2164a-h	S1	L4	M16
E2165a-h	S1	L5	M16
E2166a-h	S1	L6	M16
E2167a-h	S1	L7	M16
E2168a-h	S1	L8	M16
E2169a-h	S1	L9	M16
E2170a-h	S2	L1	M16
E2171a-h	S2	L2	M16
E2172a-h	S2	L3	M16
E2173a-h	S2	L4	M16
E2174a-h	S2	L5	M16
E2175a-h	S2	L6	M16
E2176a-h	S2	L7	M16
E2177a-h	S2	L8	M16
E2178a-h	S2	L9	M16
E2179a-h	S3	L1	M16
E2180a-h	S3	L2	M16
E2181a-h	S3	L3	M16
E2182a-h	S3	L4	M16
E2183a-h	S3	L5	M16

Example	S Group	L Group	M Group
E2184a-h	S3	L6	M16
E2185a-h	S3	L7	M16
E2186a-h	S3	L8	M16
E2187a-h	S3	L9	M16
E2188a-h	S4	L1	M16
E2189a-h	S4	L2	M16
E2190a-h	S4	L3	M16
E2191a-h	S4	L4	M16
E2192a-h	S4	L5	M16
E2193a-h	S4	L6	M16
E2194a-h	S4	L7	M16
E2195a-h	S4	L8	M16
E2196a-h	S4	L9	M16
E2197a-h	S5	L1	M16
E2198a-h	S5	L2	M16
E2199a-h	S5	L3	M16
E2200a-h	S5	L4	M16
E2201a-h	S5	L5	M16
E2202a-h	S5	L6	M16
E2203a-h	S5	L7	M16
E2204a-h	S5	L8	M16
E2205a-h	S5	L9	M16
E2206a-h	S6	L1	M16
E2207a-h	S6	L2	M16
E2208a-h	S6	L3	M16
E2209a-h	S6	L4	M16
E2210a-h	S6	L5	M16
E2211a-h	S6	L6	M16
E2212a-h	S6	L7	M16
E2213a-h	S6	L8	M16
E2214a-h	S6	L9	M16
E2215a-h	S7	L1	M16
E2216a-h	S7	L2	M16
E2217a-h	S7	L3	M16
E2218a-h	S7	L4	M16
E2219a-h	S7	L5	M16
E2220a-h	S7	L6	M16
E2221a-h	S7	L7	M16
E2222a-h	S7	L8	M16
E2223a-h	S7	L9	M16
E2224a-h	S8	L1	M16
E2225a-h	S8	L2	M16
E2226a-h	S8	L3	M16
E2227a-h	S8	L4	M16
E2228a-h	S8	L5	M16
E2229a-h	S8	L6	M16
E2230a-h	S8	L7	M16

Example	S Group	L Group	M Group
E2231a-h	S8	L8	M16
E2232a-h	S8	L9	M16
E2233a-h	S9	L1	M16
E2234a-h	S9	L2	M16
E2235a-h	S9	L3	M16
E2236a-h	S9	L4	M16
E2237a-h	S9	L5	M16
E2238a-h	S9	L6	M16
E2239a-h	S9	L7	M16
E2240a-h	S9	L8	M16
E2241a-h	S9	L9	M16
E2242a-h	S10	L1	M16
E2243a-h	S10	L2	M16
E2244a-h	S10	L3	M16
E2245a-h	S10	L4	M16
E2246a-h	S10	L5	M16
E2247a-h	S10	L6	M16
E2248a-h	S10	L7	M16
E2249a-h	S10	L8	M16
E2250a-h	S10	L9	M16
E2251a-h	S11	L1	M16
E2252a-h	S11	L2	M16
E2253a-h	S11	L3	M16
E2254a-h	S11	L4	M16
E2255a-h	S11	L5	M16
E2256a-h	S11	L6	M16
E2257a-h	S11	L7	M16
E2258a-h	S11	L8	M16
E2259a-h	S11	L9	M16
E2260a-h	S12	L1	M16
E2261a-h	S12	L2	M16
E2262a-h	S12	L3	M16
E2263a-h	S12	L4	M16
E2264a-h	S12	L5	M16
E2265a-h	S12	L6	M16
E2266a-h	S12	L7	M16
E2267a-h	S12	L8	M16
E2268a-h	S12	L9	M16
E2269a-h	S13	L1	M16
E2270a-h	S13	L2	M16
E2271a-h	S13	L3	M16
E2272a-h	S13	L4	M16
E2273a-h	S13	L5	M16
E2274a-h	S13	L6	M16
E2275a-h	S13	L7	M16
E2276a-h	S13	L8	M16
E2277a-h	S13	L9	M16

Example	S Group	L Group	M Group
E2278a-h	S14	L1	M16
E2279a-h	S14	L2	M16
E2280a-h	S14	L3	M16
E2281a-h	S14	L4	M16
E2282a-h	S14	L5	M16
E2283a-h	S14	L6	M16
E2284a-h	S14	L7	M16
E2285a-h	S14	L8	M16
E2286a-h	S14	L9	M16
E2287a-h	S15	L1	M16
E2288a-h	S15	L2	M16
E2289a-h	S15	L3	M16
E2290a-h	S15	L4	M16
E2291a-h	S15	L5	M16
E2292a-h	S15	L6	M16
E2293a-h	S15	L7	M16
E2294a-h	S15	L8	M16
E2295a-h	S15	L9	M16
E2296a-h	S16	L1	M16
E2297a-h	S16	L2	M16
E2298a-h	S16	L3	M16
E2299a-h	S16	L4	M16
E2300a-h	S16	L5	M16
E2301a-h	S16	L6	M16
E2302a-h	S16	L7	M16
E2303a-h	S16	L8	M16
E2304a-h	S16	L9	M16
E2305a-h	S1	L1	M17
E2306a-h	S1	L2	M17
E2307a-h	S1	L3	M17
E2308a-h	S1	L4	M17
E2309a-h	S1	L5	M17
E2310a-h	S1	L6	M17
E2311a-h	S1	L7	M17
E2312a-h	S1	L8	M17
E2313a-h	S1	L9	M17
E2314a-h	S2	L1	M17
E2315a-h	S2	L2	M17
E2316a-h	S2	L3	M17
E2317a-h	S2	L4	M17
E2318a-h	S2	L5	M17
E2319a-h	S2	L6	M17
E2320a-h	S2	L7	M17
E2321a-h	S2	L8	M17
E2322a-h	S2	L9	M17
E2323a-h	S3	L1	M17
E2324a-h	S3	L2	M17

Example	S Group	L Group	M Group
E2325a-h	S3	L3	M17
E2326a-h	S3	L4	M17
E2327a-h	S3	L5	M17
E2328a-h	S3	L6	M17
E2329a-h	S3	L7	M17
E2330a-h	S3	L8	M17
E2331a-h	S3	L9	M17
E2332a-h	S4	L1	M17
E2333a-h	S4	L2	M17
E2334a-h	S4	L3	M17
E2335a-h	S4	L4	M17
E2336a-h	S4	L5	M17
E2337a-h	S4	L6	M17
E2338a-h	S4	L7	M17
E2339a-h	S4	L8	M17
E2340a-h	S4	L9	M17
E2341a-h	S5	L1	M17
E2342a-h	S5	L2	M17
E2343a-h	S5	L3	M17
E2344a-h	S5	L4	M17
E2345a-h	S5	L5	M17
E2346a-h	S5	L6	M17
E2347a-h	S5	L7	M17
E2348a-h	S5	L8	M17
E2349a-h	S5	L9	M17
E2350a-h	S6	L1	M17
E2351a-h	S6	L2	M17
E2352a-h	S6	L3	M17
E2353a-h	S6	L4	M17
E2354a-h	S6	L5	M17
E2355a-h	S6	L6	M17
E2356a-h	S6	L7	M17
E2357a-h	S6	L8	M17
E2358a-h	S6	L9	M17
E2359a-h	S7	L1	M17
E2360a-h	S7	L2	M17
E2361a-h	S7	L3	M17
E2362a-h	S7	L4	M17
E2363a-h	S7	L5	M17
E2364a-h	S7	L6	M17
E2365a-h	S7	L7	M17
E2366a-h	S7	L8	M17
E2367a-h	S7	L9	M17
E2368a-h	S8	L1	M17
E2369a-h	S8	L2	M17
E2370a-h	S8	L3	M17
E2371a-h	S8	L4	M17

Example	S Group	L Group	M Group
E2372a-h	S8	L5	M17
E2373a-h	S8	L6	M17
E2374a-h	S8	L7	M17
E2375a-h	S8	L8	M17
E2376a-h	S8	L9	M17
E2377a-h	S9	L1	M17
E2378a-h	S9	L2	M17
E2379a-h	S9	L3	M17
E2380a-h	S9	L4	M17
E2381a-h	S9	L5	M17
E2382a-h	S9	L6	M17
E2383a-h	S9	L7	M17
E2384a-h	S9	L8	M17
E2385a-h	S9	L9	M17
E2386a-h	S10	L1	M17
E2387a-h	S10	L2	M17
E2388a-h	S10	L3	M17
E2389a-h	S10	L4	M17
E2390a-h	S10	L5	M17
E2391a-h	S10	L6	M17
E2392a-h	S10	L7	M17
E2393a-h	S10	L8	M17
E2394a-h	S10	L9	M17
E2395a-h	S11	L1	M17
E2396a-h	S11	L2	M17
E2397a-h	S11	L3	M17
E2398a-h	S11	L4	M17
E2399a-h	S11	L5	M17
E2400a-h	S11	L6	M17
E2401a-h	S11	L7	M17
E2402a-h	S11	L8	M17
E2403a-h	S11	L9	M17
E2404a-h	S12	L1	M17
E2405a-h	S12	L2	M17
E2406a-h	S12	L3	M17
E2407a-h	S12	L4	M17
E2408a-h	S12	L5	M17
E2409a-h	S12	L6	M17
E2410a-h	S12	L7	M17
E2411a-h	S12	L8	M17
E2412a-h	S12	L9	M17
E2413a-h	S13	L1	M17
E2414a-h	S13	L2	M17
E2415a-h	S13	L3	M17
E2416a-h	S13	L4	M17
E2417a-h	S13	L5	M17
E2418a-h	S13	L6	M17

Example	S Group	L Group	M Group
E2419a-h	S13	L7	M17
E2420a-h	S13	L8	M17
E2421a-h	S13	L9	M17
E2422a-h	S14	L1	M17
E2423a-h	S14	L2	M17
E2424a-h	S14	L3	M17
E2425a-h	S14	L4	M17
E2426a-h	S14	L5	M17
E2427a-h	S14	L6	M17
E2428a-h	S14	L7	M17
E2429a-h	S14	L8	M17
E2430a-h	S14	L9	M17
E2431a-h	S15	L1	M17
E2432a-h	S15	L2	M17
E2433a-h	S15	L3	M17
E2434a-h	S15	L4	M17
E2435a-h	S15	L5	M17
E2436a-h	S15	L6	M17
E2437a-h	S15	L7	M17
E2438a-h	S15	L8	M17
E2439a-h	S15	L9	M17
E2440a-h	S16	L1	M17
E2441a-h	S16	L2	M17
E2442a-h	S16	L3	M17
E2443a-h	S16	L4	M17
E2444a-h	S16	L5	M17
E2445a-h	S16	L6	M17
E2446a-h	S16	L7	M17
E2447a-h	S16	L8	M17
E2448a-h	S16	L9	M17
E2449a-h	S1	L1	M18
E2450a-h	S1	L2	M18
E2451a-h	S1	L3	M18
E2452a-h	S1	L4	M18
E2453a-h	S1	L5	M18
E2454a-h	S1	L6	M18
E2455a-h	S1	L7	M18
E2456a-h	S1	L8	M18
E2457a-h	S1	L9	M18
E2458a-h	S2	L1	M18
E2459a-h	S2	L2	M18
E2460a-h	S2	L3	M18
E2461a-h	S2	L4	M18
E2462a-h	S2	L5	M18
E2463a-h	S2	L6	M18
E2464a-h	S2	L7	M18
E2465a-h	S2	L8	M18

Example	S Group	L Group	M Group
E2466a-h	S2	L9	M18
E2467a-h	S3	L1	M18
E2468a-h	S3	L2	M18
E2469a-h	S3	L3	M18
E2470a-h	S3	L4	M18
E2471a-h	S3	L5	M18
E2472a-h	S3	L6	M18
E2473a-h	S3	L7	M18
E2474a-h	S3	L8	M18
E2475a-h	S3	L9	M18
E2476a-h	S4	L1	M18
E2477a-h	S4	L2	M18
E2478a-h	S4	L3	M18
E2479a-h	S4	L4	M18
E2480a-h	S4	L5	M18
E2481a-h	S4	L6	M18
E2482a-h	S4	L7	M18
E2483a-h	S4	L8	M18
E2484a-h	S4	L9	M18
E2485a-h	S5	L1	M18
E2486a-h	S5	L2	M18
E2487a-h	S5	L3	M18
E2488a-h	S5	L4	M18
E2489a-h	S5	L5	M18
E2490a-h	S5	L6	M18
E2491a-h	S5	L7	M18
E2492a-h	S5	L8	M18
E2493a-h	S5	L9	M18
E2494a-h	S6	L1	M18
E2495a-h	S6	L2	M18
E2496a-h	S6	L3	M18
E2497a-h	S6	L4	M18
E2498a-h	S6	L5	M18
E2499a-h	S6	L6	M18
E2500a-h	S6	L7	M18
E2501a-h	S6	L8	M18
E2502a-h	S6	L9	M18
E2503a-h	S7	L1	M18
E2504a-h	S7	L2	M18
E2505a-h	S7	L3	M18
E2506a-h	S7	L4	M18
E2507a-h	S7	L5	M18
E2508a-h	S7	L6	M18
E2509a-h	S7	L7	M18
E2510a-h	S7	L8	M18
E2511a-h	S7	L9	M18
E2512a-h	S8	L1	M18

Example	S Group	L Group	M Group
E2513a-h	S8	L2	M18
E2514a-h	S8	L3	M18
E2515a-h	S8	L4	M18
E2516a-h	S8	L5	M18
E2517a-h	S8	L6	M18
E2518a-h	S8	L7	M18
E2519a-h	S8	L8	M18
E2520a-h	S8	L9	M18
E2521a-h	S9	L1	M18
E2522a-h	S9	L2	M18
E2523a-h	S9	L3	M18
E2524a-h	S9	L4	M18
E2525a-h	S9	L5	M18
E2526a-h	S9	L6	M18
E2527a-h	S9	L7	M18
E2528a-h	S9	L8	M18
E2529a-h	S9	L9	M18
E2530a-h	S10	L1	M18
E2531a-h	S10	L2	M18
E2532a-h	S10	L3	M18
E2533a-h	S10	L4	M18
E2534a-h	S10	L5	M18
E2535a-h	S10	L6	M18
E2536a-h	S10	L7	M18
E2537a-h	S10	L8	M18
E2538a-h	S10	L9	M18
E2539a-h	S11	L1	M18
E2540a-h	S11	L2	M18
E2541a-h	S11	L3	M18
E2542a-h	S11	L4	M18
E2543a-h	S11	L5	M18
E2544a-h	S11	L6	M18
E2545a-h	S11	L7	M18
E2546a-h	S11	L8	M18
E2547a-h	S11	L9	M18
E2548a-h	S12	L1	M18
E2549a-h	S12	L2	M18
E2550a-h	S12	L3	M18
E2551a-h	S12	L4	M18
E2552a-h	S12	L5	M18
E2553a-h	S12	L6	M18
E2554a-h	S12	L7	M18
E2555a-h	S12	L8	M18
E2556a-h	S12	L9	M18
E2557a-h	S13	L1	M18
E2558a-h	S13	L2	M18
E2559a-h	S13	L3	M18

Example	S Group	L Group	M Group
E2560a-h	S13	L4	M18
E2561a-h	S13	L5	M18
E2562a-h	S13	L6	M18
E2563a-h	S13	L7	M18
E2564a-h	S13	L8	M18
E2565a-h	S13	L9	M18
E2566a-h	S14	L1	M18
E2567a-h	S14	L2	M18
E2568a-h	S14	L3	M18
E2569a-h	S14	L4	M18
E2570a-h	S14	L5	M18
E2571a-h	S14	L6	M18
E2572a-h	S14	L7	M18
E2573a-h	S14	L8	M18
E2574a-h	S14	L9	M18
E2575a-h	S15	L1	M18
E2576a-h	S15	L2	M18
E2577a-h	S15	L3	M18
E2578a-h	S15	L4	M18
E2579a-h	S15	L5	M18
E2580a-h	S15	L6	M18
E2581a-h	S15	L7	M18
E2582a-h	S15	L8	M18
E2583a-h	S15	L9	M18
E2584a-h	S16	L1	M18
E2585a-h	S16	L2	M18
E2586a-h	S16	L3	M18
E2587a-h	S16	L4	M18
E2588a-h	S16	L5	M18
E2589a-h	S16	L6	M18
E2590a-h	S16	L7	M18
E2591a-h	S16	L8	M18
E2592a-h	S16	L9	M18
E2593a-h	S1	L1	M19
E2594a-h	S1	L2	M19
E2595a-h	S1	L3	M19
E2596a-h	S1	L4	M19
E2597a-h	S1	L5	M19
E2598a-h	S1	L6	M19
E2599a-h	S1	L7	M19
E2600a-h	S1	L8	M19
E2601a-h	S1	L9	M19
E2602a-h	S2	L1	M19
E2603a-h	S2	L2	M19
E2604a-h	S2	L3	M19
E2605a-h	S2	L4	M19
E2606a-h	S2	L5	M19

Example	S Group	L Group	M Group
E2607a-h	S2	L6	M19
E2608a-h	S2	L7	M19
E2609a-h	S2	L8	M19
E2610a-h	S2	L9	M19
E2611a-h	S3	L1	M19
E2612a-h	S3	L2	M19
E2613a-h	S3	L3	M19
E2614a-h	S3	L4	M19
E2615a-h	S3	L5	M19
E2616a-h	S3	L6	M19
E2617a-h	S3	L7	M19
E2618a-h	S3	L8	M19
E2619a-h	S3	L9	M19
E2620a-h	S4	L1	M19
E2621a-h	S4	L2	M19
E2622a-h	S4	L3	M19
E2623a-h	S4	L4	M19
E2624a-h	S4	L5	M19
E2625a-h	S4	L6	M19
E2626a-h	S4	L7	M19
E2627a-h	S4	L8	M19
E2628a-h	S4	L9	M19
E2629a-h	S5	L1	M19
E2630a-h	S5	L2	M19
E2631a-h	S5	L3	M19
E2632a-h	S5	L4	M19
E2633a-h	S5	L5	M19
E2634a-h	S5	L6	M19
E2635a-h	S5	L7	M19
E2636a-h	S5	L8	M19
E2637a-h	S5	L9	M19
E2638a-h	S6	L1	M19
E2639a-h	S6	L2	M19
E2640a-h	S6	L3	M19
E2641a-h	S6	L4	M19
E2642a-h	S6	L5	M19
E2643a-h	S6	L6	M19
E2644a-h	S6	L7	M19
E2645a-h	S6	L8	M19
E2646a-h	S6	L9	M19
E2647a-h	S7	L1	M19
E2648a-h	S7	L2	M19
E2649a-h	S7	L3	M19
E2650a-h	S7	L4	M19
E2651a-h	S7	L5	M19
E2652a-h	S7	L6	M19
E2653a-h	S7	L7	M19

Example	S Group	L Group	M Group
E2654a-h	S7	L8	M19
E2655a-h	S7	L9	M19
E2656a-h	S8	L1	M19
E2657a-h	S8	L2	M19
E2658a-h	S8	L3	M19
E2659a-h	S8	L4	M19
E2660a-h	S8	L5	M19
E2661a-h	S8	L6	M19
E2662a-h	S8	L7	M19
E2663a-h	S8	L8	M19
E2664a-h	S8	L9	M19
E2665a-h	S9	L1	M19
E2666a-h	S9	L2	M19
E2667a-h	S9	L3	M19
E2668a-h	S9	L4	M19
E2669a-h	S9	L5	M19
E2670a-h	S9	L6	M19
E2671a-h	S9	L7	M19
E2672a-h	S9	L8	M19
E2673a-h	S9	L9	M19
E2674a-h	S10	L1	M19
E2675a-h	S10	L2	M19
E2676a-h	S10	L3	M19
E2677a-h	S10	L4	M19
E2678a-h	S10	L5	M19
E2679a-h	S10	L6	M19
E2680a-h	S10	L7	M19
E2681a-h	S10	L8	M19
E2682a-h	S10	L9	M19
E2683a-h	S11	L1	M19
E2684a-h	S11	L2	M19
E2685a-h	S11	L3	M19
E2686a-h	S11	L4	M19
E2687a-h	S11	L5	M19
E2688a-h	S11	L6	M19
E2689a-h	S11	L7	M19
E2690a-h	S11	L8	M19
E2691a-h	S11	L9	M19
E2692a-h	S12	L1	M19
E2693a-h	S12	L2	M19
E2694a-h	S12	L3	M19
E2695a-h	S12	L4	M19
E2696a-h	S12	L5	M19
E2697a-h	S12	L6	M19
E2698a-h	S12	L7	M19
E2699a-h	S12	L8	M19
E2700a-h	S12	L9	M19

Example	S Group	L Group	M Group
E2701a-h	S13	L1	M19
E2702a-h	S13	L2	M19
E2703a-h	S13	L3	M19
E2704a-h	S13	L4	M19
E2705a-h	S13	L5	M19
E2706a-h	S13	L6	M19
E2707a-h	S13	L7	M19
E2708a-h	S13	L8	M19
E2709a-h	S13	L9	M19
E2710a-h	S14	L1	M19
E2711a-h	S14	L2	M19
E2712a-h	S14	L3	M19
E2713a-h	S14	L4	M19
E2714a-h	S14	L5	M19
E2715a-h	S14	L6	M19
E2716a-h	S14	L7	M19
E2717a-h	S14	L8	M19
E2718a-h	S14	L9	M19
E2719a-h	S15	L1	M19
E2720a-h	S15	L2	M19
E2721a-h	S15	L3	M19
E2722a-h	S15	L4	M19
E2723a-h	S15	L5	M19
E2724a-h	S15	L6	M19
E2725a-h	S15	L7	M19
E2726a-h	S15	L8	M19
E2727a-h	S15	L9	M19
E2728a-h	S16	L1	M19
E2729a-h	S16	L2	M19
E2730a-h	S16	L3	M19
E2731a-h	S16	L4	M19
E2732a-h	S16	L5	M19
E2733a-h	S16	L6	M19
E2734a-h	S16	L7	M19
E2735a-h	S16	L8	M19
E2736a-h	S16	L9	M19
E2737a-h	S1	L1	M20
E2738a-h	S1	L2	M20
E2739a-h	S1	L3	M20
E2740a-h	S1	L4	M20
E2741a-h	S1	L5	M20
E2742a-h	S1	L6	M20
E2743a-h	S1	L7	M20
E2744a-h	S1	L8	M20
E2745a-h	S1	L9	M20
E2746a-h	S2	L1	M20
E2747a-h	S2	L2	M20

Example	S Group	L Group	M Group
E2748a-h	S2	L3	M20
E2749a-h	S2	L4	M20
E2750a-h	S2	L5	M20
E2751a-h	S2	L6	M20
E2752a-h	S2	L7	M20
E2753a-h	S2	L8	M20
E2754a-h	S2	L9	M20
E2755a-h	S3	L1	M20
E2756a-h	S3	L2	M20
E2757a-h	S3	L3	M20
E2758a-h	S3	L4	M20
E2759a-h	S3	L5	M20
E2760a-h	S3	L6	M20
E2761a-h	S3	L7	M20
E2762a-h	S3	L8	M20
E2763a-h	S3	L9	M20
E2764a-h	S4	L1	M20
E2765a-h	S4	L2	M20
E2766a-h	S4	L3	M20
E2767a-h	S4	L4	M20
E2768a-h	S4	L5	M20
E2769a-h	S4	L6	M20
E2770a-h	S4	L7	M20
E2771a-h	S4	L8	M20
E2772a-h	S4	L9	M20
E2773a-h	S5	L1	M20
E2774a-h	S5	L2	M20
E2775a-h	S5	L3	M20
E2776a-h	S5	L4	M20
E2777a-h	S5	L5	M20
E2778a-h	S5	L6	M20
E2779a-h	S5	L7	M20
E2780a-h	S5	L8	M20
E2781a-h	S5	L9	M20
E2782a-h	S6	L1	M20
E2783a-h	S6	L2	M20
E2784a-h	S6	L3	M20
E2785a-h	S6	L4	M20
E2786a-h	S6	L5	M20
E2787a-h	S6	L6	M20
E2788a-h	S6	L7	M20
E2789a-h	S6	L8	M20
E2790a-h	S6	L9	M20
E2791a-h	S7	L1	M20
E2792a-h	S7	L2	M20
E2793a-h	S7	L3	M20
E2794a-h	S7	L4	M20

Example	S Group	L Group	M Group
E2795a-h	S7	L5	M20
E2796a-h	S7	L6	M20
E2797a-h	S7	L7	M20
E2798a-h	S7	L8	M20
E2799a-h	S7	L9	M20
E2800a-h	S8	L1	M20
E2801a-h	S8	L2	M20
E2802a-h	S8	L3	M20
E2803a-h	S8	L4	M20
E2804a-h	S8	L5	M20
E2805a-h	S8	L6	M20
E2806a-h	S8	L7	M20
E2807a-h	S8	L8	M20
E2808a-h	S8	L9	M20
E2809a-h	S9	L1	M20
E2810a-h	S9	L2	M20
E2811a-h	S9	L3	M20
E2812a-h	S9	L4	M20
E2813a-h	S9	L5	M20
E2814a-h	S9	L6	M20
E2815a-h	S9	L7	M20
E2816a-h	S9	L8	M20
E2817a-h	S9	L9	M20
E2818a-h	S10	L1	M20
E2819a-h	S10	L2	M20
E2820a-h	S10	L3	M20
E2821a-h	S10	L4	M20
E2822a-h	S10	L5	M20
E2823a-h	S10	L6	M20
E2824a-h	S10	L7	M20
E2825a-h	S10	L8	M20
E2826a-h	S10	L9	M20
E2827a-h	S11	L1	M20
E2828a-h	S11	L2	M20
E2829a-h	S11	L3	M20
E2830a-h	S11	L4	M20
E2831a-h	S11	L5	M20
E2832a-h	S11	L6	M20
E2833a-h	S11	L7	M20
E2834a-h	S11	L8	M20
E2835a-h	S11	L9	M20
E2836a-h	S12	L1	M20
E2837a-h	S12	L2	M20
E2838a-h	S12	L3	M20
E2839a-h	S12	L4	M20
E2840a-h	S12	L5	M20
E2841a-h	S12	L6	M20

Example	S Group	L Group	M Group
E2842a-h	S12	L7	M20
E2843a-h	S12	L8	M20
E2844a-h	S12	L9	M20
E2845a-h	S13	L1	M20
E2846a-h	S13	L2	M20
E2847a-h	S13	L3	M20
E2848a-h	S13	L4	M20
E2849a-h	S13	L5	M20
E2850a-h	S13	L6	M20
E2851a-h	S13	L7	M20
E2852a-h	S13	L8	M20
E2853a-h	S13	L9	M20
E2854a-h	S14	L1	M20
E2855a-h	S14	L2	M20
E2856a-h	S14	L3	M20
E2857a-h	S14	L4	M20
E2858a-h	S14	L5	M20
E2859a-h	S14	L6	M20
E2860a-h	S14	L7	M20
E2861a-h	S14	L8	M20
E2862a-h	S14	L9	M20
E2863a-h	S15	L1	M20
E2864a-h	S15	L2	M20
E2865a-h	S15	L3	M20
E2866a-h	S15	L4	M20
E2867a-h	S15	L5	M20
E2868a-h	S15	L6	M20
E2869a-h	S15	L7	M20
E2870a-h	S15	L8	M20
E2871a-h	S15	L9	M20
E2872a-h	S16	L1	M20
E2873a-h	S16	L2	M20
E2874a-h	S16	L3	M20
E2875a-h	S16	L4	M20
E2876a-h	S16	L5	M20
E2877a-h	S16	L6	M20
E2878a-h	S16	L7	M20
E2879a-h	S16	L8	M20
E2880a-h	S16	L9	M20
E2881a-h	S1	L1	M21
E2882a-h	S1	L2	M21
E2883a-h	S1	L3	M21
E2884a-h	S1	L4	M21
E2885a-h	S1	L5	M21
E2886a-h	S1	L6	M21
E2887a-h	S1	L7	M21
E2888a-h	S1	L8	M21

Example	S Group	L Group	M Group
E2889a-h	S1	L9	M21
E2890a-h	S2	L1	M21
E2891a-h	S2	L2	M21
E2892a-h	S2	L3	M21
E2893a-h	S2	L4	M21
E2894a-h	S2	L5	M21
E2895a-h	S2	L6	M21
E2896a-h	S2	L7	M21
E2897a-h	S2	L8	M21
E2898a-h	S2	L9	M21
E2899a-h	S3	L1	M21
E2900a-h	S3	L2	M21
E2901a-h	S3	L3	M21
E2902a-h	S3	L4	M21
E2903a-h	S3	L5	M21
E2904a-h	S3	L6	M21
E2905a-h	S3	L7	M21
E2906a-h	S3	L8	M21
E2907a-h	S3	L9	M21
E2908a-h	S4	L1	M21
E2909a-h	S4	L2	M21
E2910a-h	S4	L3	M21
E2911a-h	S4	L4	M21
E2912a-h	S4	L5	M21
E2913a-h	S4	L6	M21
E2914a-h	S4	L7	M21
E2915a-h	S4	L8	M21
E2916a-h	S4	L9	M21
E2917a-h	S5	L1	M21
E2918a-h	S5	L2	M21
E2919a-h	S5	L3	M21
E2920a-h	S5	L4	M21
E2921a-h	S5	L5	M21
E2922a-h	S5	L6	M21
E2923a-h	S5	L7	M21
E2924a-h	S5	L8	M21
E2925a-h	S5	L9	M21
E2926a-h	S6	L1	M21
E2927a-h	S6	L2	M21
E2928a-h	S6	L3	M21
E2929a-h	S6	L4	M21
E2930a-h	S6	L5	M21
E2931a-h	S6	L6	M21
E2932a-h	S6	L7	M21
E2933a-h	S6	L8	M21
E2934a-h	S6	L9	M21
E2935a-h	S7	L1	M21

Example	S Group	L Group	M Group
E2936a-h	S7	L2	M21
E2937a-h	S7	L3	M21
E2938a-h	S7	L4	M21
E2939a-h	S7	L5	M21
E2940a-h	S7	L6	M21
E2941a-h	S7	L7	M21
E2942a-h	S7	L8	M21
E2943a-h	S7	L9	M21
E2944a-h	S8	L1	M21
E2945a-h	S8	L2	M21
E2946a-h	S8	L3	M21
E2947a-h	S8	L4	M21
E2948a-h	S8	L5	M21
E2949a-h	S8	L6	M21
E2950a-h	S8	L7	M21
E2951a-h	S8	L8	M21
E2952a-h	S8	L9	M21
E2953a-h	S9	L1	M21
E2954a-h	S9	L2	M21
E2955a-h	S9	L3	M21
E2956a-h	S9	L4	M21
E2957a-h	S9	L5	M21
E2958a-h	S9	L6	M21
E2959a-h	S9	L7	M21
E2960a-h	S9	L8	M21
E2961a-h	S9	L9	M21
E2962a-h	S10	L1	M21
E2963a-h	S10	L2	M21
E2964a-h	S10	L3	M21
E2965a-h	S10	L4	M21
E2966a-h	S10	L5	M21
E2967a-h	S10	L6	M21
E2968a-h	S10	L7	M21
E2969a-h	S10	L8	M21
E2970a-h	S10	L9	M21
E2971a-h	S11	L1	M21
E2972a-h	S11	L2	M21
E2973a-h	S11	L3	M21
E2974a-h	S11	L4	M21
E2975a-h	S11	L5	M21
E2976a-h	S11	L6	M21
E2977a-h	S11	L7	M21
E2978a-h	S11	L8	M21
E2979a-h	S11	L9	M21
E2980a-h	S12	L1	M21
E2981a-h	S12	L2	M21
E2982a-h	S12	L3	M21

Example	S Group	L Group	M Group
E2983a-h	S12	L4	M21
E2984a-h	S12	L5	M21
E2985a-h	S12	L6	M21
E2986a-h	S12	L7	M21
E2987a-h	S12	L8	M21
E2988a-h	S12	L9	M21
E2989a-h	S13	L1	M21
E2990a-h	S13	L2	M21
E2991a-h	S13	L3	M21
E2992a-h	S13	L4	M21
E2993a-h	S13	L5	M21
E2994a-h	S13	L6	M21
E2995a-h	S13	L7	M21
E2996a-h	S13	L8	M21
E2997a-h	S13	L9	M21
E2998a-h	S14	L1	M21
E2999a-h	S14	L2	M21
E3000a-h	S14	L3	M21
E3001a-h	S14	L4	M21
E3002a-h	S14	L5	M21
E3003a-h	S14	L6	M21
E3004a-h	S14	L7	M21
E3005a-h	S14	L8	M21
E3006a-h	S14	L9	M21
E3007a-h	S15	L1	M21
E3008a-h	S15	L2	M21
E3009a-h	S15	L3	M21
E3010a-h	S15	L4	M21
E3011a-h	S15	L5	M21
E3012a-h	S15	L6	M21
E3013a-h	S15	L7	M21
E3014a-h	S15	L8	M21
E3015a-h	S15	L9	M21
E3016a-h	S16	L1	M21
E3017a-h	S16	L2	M21
E3018a-h	S16	L3	M21
E3019a-h	S16	L4	M21
E3020a-h	S16	L5	M21
E3021a-h	S16	L6	M21
E3022a-h	S16	L7	M21
E3023a-h	S16	L8	M21
E3024a-h	S16	L9	M21
E3025a-h	S1	L1	M22
E3026a-h	S1	L2	M22
E3027a-h	S1	L3	M22
E3028a-h	S1	L4	M22
E3029a-h	S1	L5	M22

Example	S Group	L Group	M Group
E3030a-h	S1	L6	M22
E3031a-h	S1	L7	M22
E3032a-h	S1	L8	M22
E3033a-h	S1	L9	M22
E3034a-h	S2	L1	M22
E3035a-h	S2	L2	M22
E3036a-h	S2	L3	M22
E3037a-h	S2	L4	M22
E3038a-h	S2	L5	M22
E3039a-h	S2	L6	M22
E3040a-h	S2	L7	M22
E3041a-h	S2	L8	M22
E3042a-h	S2	L9	M22
E3043a-h	S3	L1	M22
E3044a-h	S3	L2	M22
E3045a-h	S3	L3	M22
E3046a-h	S3	L4	M22
E3047a-h	S3	L5	M22
E3048a-h	S3	L6	M22
E3049a-h	S3	L7	M22
E3050a-h	S3	L8	M22
E3051a-h	S3	L9	M22
E3052a-h	S4	L1	M22
E3053a-h	S4	L2	M22
E3054a-h	S4	L3	M22
E3055a-h	S4	L4	M22
E3056a-h	S4	L5	M22
E3057a-h	S4	L6	M22
E3058a-h	S4	L7	M22
E3059a-h	S4	L8	M22
E3060a-h	S4	L9	M22
E3061a-h	S5	L1	M22
E3062a-h	S5	L2	M22
E3063a-h	S5	L3	M22
E3064a-h	S5	L4	M22
E3065a-h	S5	L5	M22
E3066a-h	S5	L6	M22
E3067a-h	S5	L7	M22
E3068a-h	S5	L8	M22
E3069a-h	S5	L9	M22
E3070a-h	S6	L1	M22
E3071a-h	S6	L2	M22
E3072a-h	S6	L3	M22
E3073a-h	S6	L4	M22
E3074a-h	S6	L5	M22
E3075a-h	S6	L6	M22
E3076a-h	S6	L7	M22

Example	S Group	L Group	M Group
E3077a-h	S6	L8	M22
E3078a-h	S6	L9	M22
E3079a-h	S7	L1	M22
E3080a-h	S7	L2	M22
E3081a-h	S7	L3	M22
E3082a-h	S7	L4	M22
E3083a-h	S7	L5	M22
E3084a-h	S7	L6	M22
E3085a-h	S7	L7	M22
E3086a-h	S7	L8	M22
E3087a-h	S7	L9	M22
E3088a-h	S8	L1	M22
E3089a-h	S8	L2	M22
E3090a-h	S8	L3	M22
E3091a-h	S8	L4	M22
E3092a-h	S8	L5	M22
E3093a-h	S8	L6	M22
E3094a-h	S8	L7	M22
E3095a-h	S8	L8	M22
E3096a-h	S8	L9	M22
E3097a-h	S9	L1	M22
E3098a-h	S9	L2	M22
E3099a-h	S9	L3	M22
E3100a-h	S9	L4	M22
E3101a-h	S9	L5	M22
E3102a-h	S9	L6	M22
E3103a-h	S9	L7	M22
E3104a-h	S9	L8	M22
E3105a-h	S9	L9	M22
E3106a-h	S10	L1	M22
E3107a-h	S10	L2	M22
E3108a-h	S10	L3	M22
E3109a-h	S10	L4	M22
E3110a-h	S10	L5	M22
E3111a-h	S10	L6	M22
E3112a-h	S10	L7	M22
E3113a-h	S10	L8	M22
E3114a-h	S10	L9	M22
E3115a-h	S11	L1	M22
E3116a-h	S11	L2	M22
E3117a-h	S11	L3	M22
E3118a-h	S11	L4	M22
E3119a-h	S11	L5	M22
E3120a-h	S11	L6	M22
E3121a-h	S11	L7	M22
E3122a-h	S11	L8	M22
E3123a-h	S11	L9	M22

Example	S Group	L Group	M Group
E3124a-h	S12	L1	M22
E3125a-h	S12	L2	M22
E3126a-h	S12	L3	M22
E3127a-h	S12	L4	M22
E3128a-h	S12	L5	M22
E3129a-h	S12	L6	M22
E3130a-h	S12	L7	M22
E3131a-h	S12	L8	M22
E3132a-h	S12	L9	M22
E3133a-h	S13	L1	M22
E3134a-h	S13	L2	M22
E3135a-h	S13	L3	M22
E3136a-h	S13	L4	M22
E3137a-h	S13	L5	M22
E3138a-h	S13	L6	M22
E3139a-h	S13	L7	M22
E3140a-h	S13	L8	M22
E3141a-h	S13	L9	M22
E3142a-h	S14	L1	M22
E3143a-h	S14	L2	M22
E3144a-h	S14	L3	M22
E3145a-h	S14	L4	M22
E3146a-h	S14	L5	M22
E3147a-h	S14	L6	M22
E3148a-h	S14	L7	M22
E3149a-h	S14	L8	M22
E3150a-h	S14	L9	M22
E3151a-h	S15	L1	M22
E3152a-h	S15	L2	M22
E3153a-h	S15	L3	M22
E3154a-h	S15	L4	M22
E3155a-h	S15	L5	M22
E3156a-h	S15	L6	M22
E3157a-h	S15	L7	M22
E3158a-h	S15	L8	M22
E3159a-h	S15	L9	M22
E3160a-h	S16	L1	M22
E3161a-h	S16	L2	M22
E3162a-h	S16	L3	M22
E3163a-h	S16	L4	M22
E3164a-h	S16	L5	M22
E3165a-h	S16	L6	M22
E3166a-h	S16	L7	M22
E3167a-h	S16	L8	M22
E3168a-h	S16	L9	M22

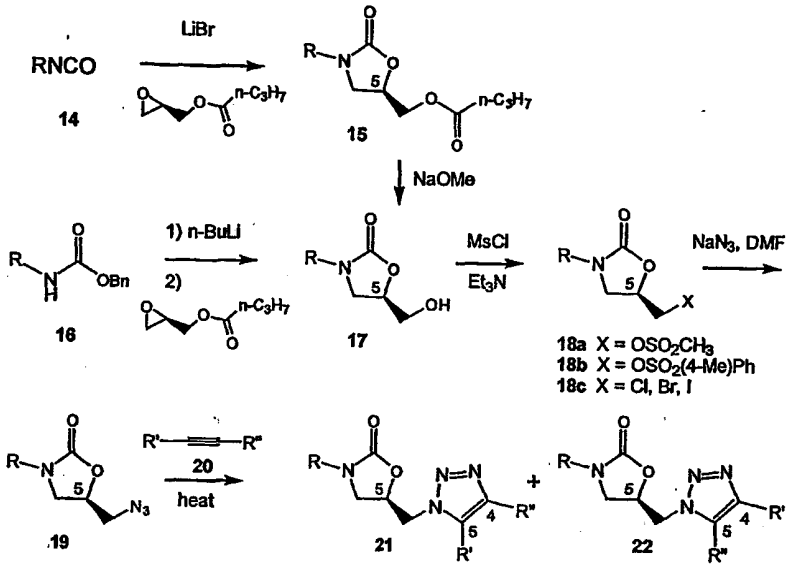
3. Synthesis of the Compounds of the Invention

In another aspect, the invention provides methods for making the compounds of the invention. The following schemes depict some exemplary chemistry available for synthesizing compounds of the invention. It will be appreciated, however, that the desired compounds may be synthesized using other alternative chemistries known in the art.

Scheme 1 illustrates the synthesis of oxazolidinones substituted at C-5 with 1,2,3-triazolylmethyl derivatives. Isocyanates **14** can react with lithium bromide and glycidyl butyrate at elevated temperature to produce oxazolidinone intermediates of type **15** (Gregory *et al.* (1989) J. MED. CHEM. 32: 1673). Hydrolysis of the resulting butyrate ester of compound **15** produces alcohol **17**. Alcohol **17** can also be synthesized from carbamates such as the benzyl carbamate **16**. The carbamate nitrogen of compound **16** then is deprotonated, and alkylated with glycidyl butyrate to produce (after *in situ* hydrolysis of the butyl ester) hydroxymethyl derivative **17**. While the R enantiomer depicted throughout Scheme 1 generally is the most biologically useful derivative for antibacterial agents, it is contemplated that compounds derived from either the R or the S enantiomer, or any mixture of R and S enantiomers, may be useful in the practice of the invention.

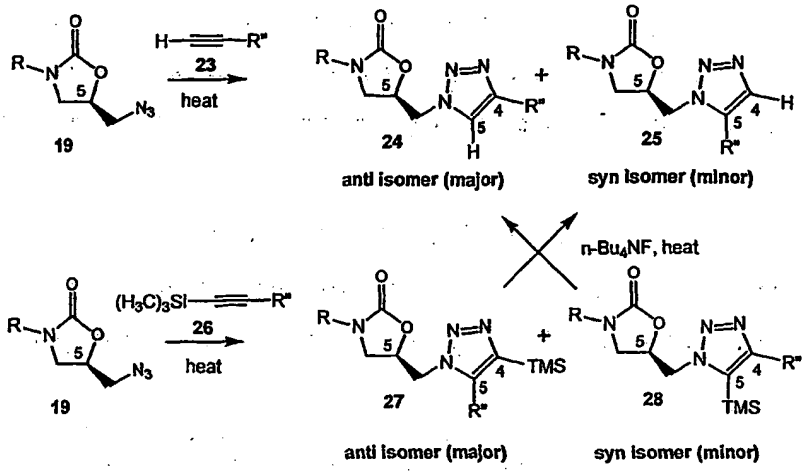
Alcohols **17** can be converted to useful intermediates such as mesylates **18a** (by treatment with methanesulfonyl chloride and triethylamine in an appropriate solvent) and azide **19** (by subsequent displacement of the mesylate by sodium azide in DMF). Azide **19** can also be produced from tosylate **18b** (or a brosylate or nosylate), or an alkyl halide of type **18c** (made from alcohol **17** via methods known to those skilled in the art). Azide **19** can be heated in the presence of substituted acetylenes **20** to produce C-5 substituted 1,2,3-triazolylmethyl oxazolidinone derivatives of type **21** and **22**. It is to be understood that alternative chemical conditions could be employed by those skilled in the art to effect this transformation.

Scheme 1



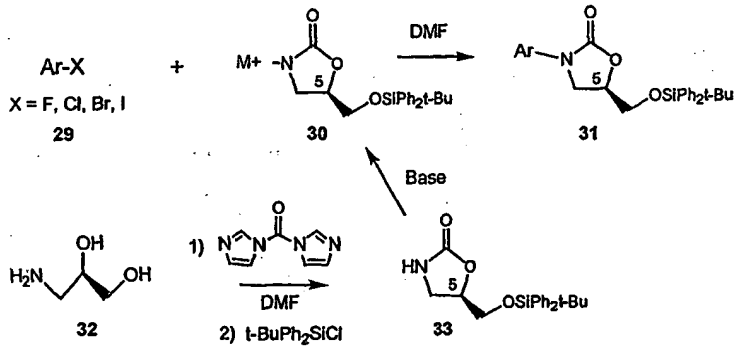
It is understood that unsymmetrical acetylene derivatives can react to produce a mixture of regioisomeric cycloaddition products, represented by **21** and **22**, and that the reaction conditions can be adjusted by processes known to those skilled in the art to produce more selectively one regioisomer or the other. For example, Scheme 2 depicts the reaction of mono-substituted acetylene **23** with azide **19** to produce two regioisomeric triazoles, **24** and **25**. The major isomer is most often the anti isomer **24** since the reaction leading to this product proceeds at a faster rate. Under certain circumstances, the more sterically disfavored syn isomer is also formed, but at an appreciably diminished rate. The addition of copper(I)iodide is a useful additive for this reaction, and often leads to increased proportions of the major "anti" adduct **24** (Tornoe, C.W. *et al.* (2002) J. ORG. CHEM. 67: 3057). Increased proportions of the minor isomer **25** may be produced by minor modification of the reaction scheme. Azide **19** can react with the trimethylsilyl substituted acetylene **26** to produce the anti isomer **27** and the syn isomer **28**. Desilylation with tetrabutylammonium fluoride can produce triazole **24** and **25**, with increased proportions of **25** obtainable from the more abundant precursor triazole **27**.

Scheme 2



An alternate approach toward the synthesis of some of the compounds of the present invention is shown in Scheme 3a. Aromatic halide **29**, when activated, can react with the anion derived from treatment of carbamate **33** with an appropriate base to produce 3-aryl substituted oxazolidinone derivatives **31** via nucleophilic aromatic substitution. Suitable bases include, for example, n-BuLi, $LiN(Si(CH_3)_3)_2$, and NaH. Carbamate **33** can be synthesized by exposure of **32** to carbonyldiimidazole in DMF, followed by *in situ* silylation of the hydroxymethyl group of the initial product with an appropriate silyl chloride. Desilylation of derivatives of type **31** produces alcohols **17** that can be converted to the targets of the present invention by the processes described within the schemes.

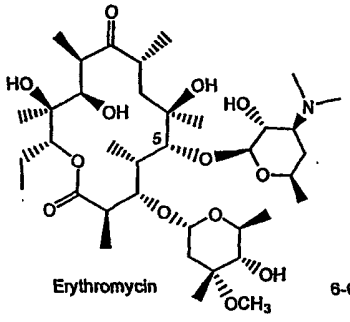
Scheme 3a

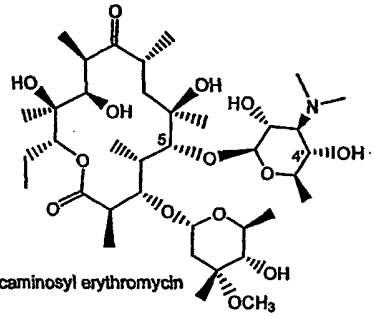


Erythromycin, as will be noted from the formula below, comprises three cyclic fragments. These fragments are referred to respectively as cladinose, desosamine and erythronolide. The naturally occurring compound erythromycin and most of its useful synthetic derivatives have the sugar desosamine attached to the C-5 oxygen of the macrolide ring.

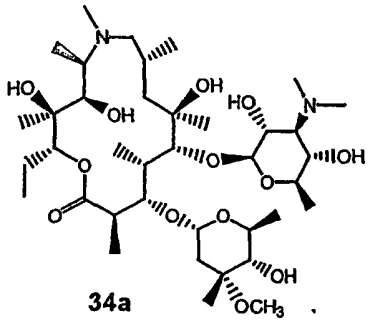
Compounds of the present invention possess an additional oxygen substituent at the 4' position of the desosamine, i.e., they possess the sugar myaminose at the C-5 position in place of desosamine. In the present invention, all substitution takes place at the 4' position of the desosamine moiety. Erythromycin possessing this alternate sugar was first described in 1969 in U.S. Patent No. 3,629,232.

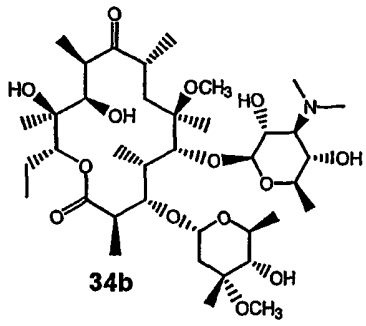
The first step in preparing the compounds of this invention is to prepare 4'-hydroxyerthromycin. A preparative scheme for obtaining the 4'-hydroxyerthromycin is set forth in U.S. Patent Application Serial No. 807,444, filed March 14, 1969, and now abandoned.

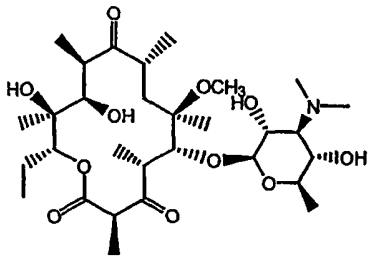




6-O-mycaminosyl-erythromycin has very similar chemical reactivity to erythromycin itself and, therefore, may be treated according to known methodology practiced on erythromycin to produce numerous useful analogs, including, for example: 6-O-mycaminosyl azithromycin, **(34a)**, 6-O-mycaminosyl clarithromycin **(34b)**, and 6-O-mycaminosyl clarithromycin 3-ketolide. **(34c)**.

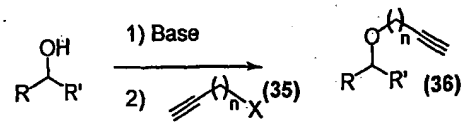

34a


34b


34c

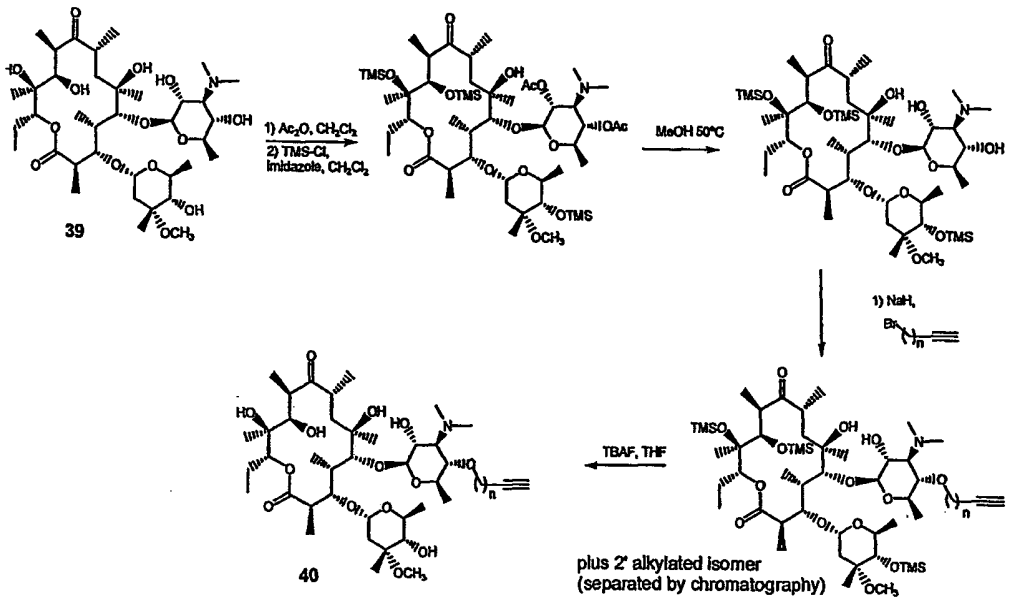
Compounds 34a, 34b, and 34c can be produced from 6-mycaminosyl erythromycin using the procedures described in U.S. Patent Nos. 6,013,778, 5,852,180, and 5,444,051, respectively.

Secondary alcohols (or cycloalkyl alcohols) can be alkylated with electrophiles having an alkyne connected by a variable bond or linker to a carbon bearing a leaving group, for example, a halide or a sulfonate group **35**, to produce ethers of type **36**.



It is necessary to alkylate the 4'-hydroxyl group of the mycaminose sugar to produce compounds of the present invention from 3-mycamynosyl erythromycin or its derivatives. This is accomplished as presented in Scheme 3b. Briefly, the 2' and 4' hydroxyl groups of 3-mycaminosyl erythromycin can be selectively acylated by acid anhydrides in the absence of added base without causing reaction of the other hydroxyl groups of the molecule (e.g. 4''-OH, 11-OH, and 12-OH). This selectivity is possible because of the influence of the adjacent tertiary amine at the 3' position. The remaining hydroxy groups are then protected for instance as their trimethylsilyl ethers. The acyl groups on the 2' and 4' hydroxyl groups are then removed selectively under mild conditions and the 4' hydroxyl group is alkylated. Reaction of either the 4' or 2' oxygen without also affecting the other is typically difficult. The schemes shown below rely on the physical separation of the regioisomers obtained after such reactions when it is desired to have only the 4' hydroxyl group substituted. Though not always explicitly shown, it is to be understood that the reaction conditions employed can cause reaction at both the 2' and 4' hydroxyl groups and that the desired 4'-substituted product is separated from other products in the crude reaction mixture.

Scheme 3b

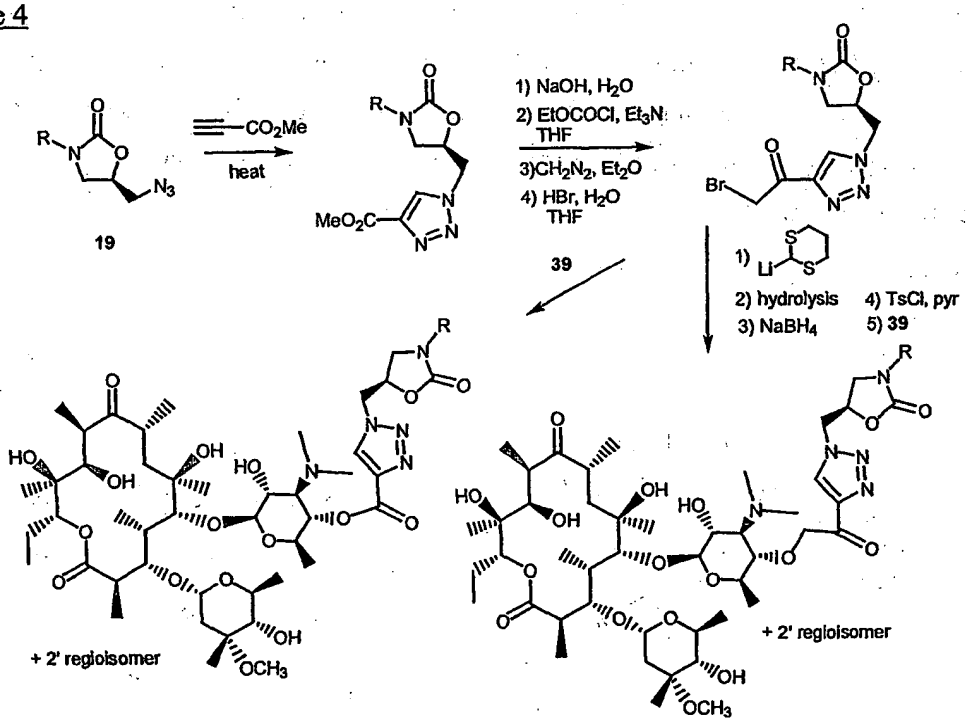


In the present case, it is necessary to protect other hydroxyl moieties in 6-mycaminosyl erythromycin from reaction. One method of accomplishing this end is presented in Scheme 3b. Since the 2' and 4' hydroxyl groups are the most reactive toward acylation, they are first selectively protected as esters (i.e. acetate, propionate, benzoate, trifluoroacetate etc.) by reaction with an excess of a suitable acid anhydride in an inert solvent. The remaining reactive hydroxy groups are then protected as their silyl ethers, for example, trimethyl silyl, triethyl silyl, or tert-butyldimethyl silyl ether. The 6 hydroxyl moiety is sterically hindered and does not normally react under the conditions used in the schemes. The acyl protecting groups on the 2' and 4' oxygens can subsequently be removed under conditions that do not affect the silyl ethers, e.g. basic hydrolysis, and methanolysis. With the 4'', 11, and 12 hydroxy groups thus protected, selective alkylation the 4' oxygen can be achieved under standard alkylating conditions. Many other protecting groups can be successfully employed to accomplish a similar outcome. See, e.g., T.H. Greene and P.G.M. Wuts (1999) PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, 3rd edition, John Wiley & Sons, New York.

Furthermore, it is understood that, given appropriate reaction conditions known to those skilled in the art, any similarly substituted macrolide antibacterial agent (naturally occurring, semi-synthetic or synthesized) is capable of serving as starting material for the processes depicted in Scheme 3b. The substituted alkynes 40 thereby obtained can be used in cycloaddition reactions with azides to yield triazole-linked target compounds.

Scheme 4 illustrates the synthesis of compounds of the present invention that contain extra keto groups in the alkyl link between the 5-membered heterocyclic ring and the macrolide moiety. Azides **19** can react with propiolate esters to produce the ester-substituted products. It is to be understood that mixtures of regioisomeric cycloadducts may form in this reaction, however, only the anti adduct is depicted in Scheme 4b. Hydrolysis of the ester yields the acid, which can be converted using known chemistry (Ramtohul *et al.* (2000) J. ORG. CHEM. 67: 3169) to the bromoacetyl triazole. Heating this bromoacetyl derivative with **39** (or a suitably protected version of **39**) can yield products that contain a keto link with one methylene group between the ketone and the macrolide group. The bromoacetyl intermediate can be converted via lithio-dithiane chemistry, subsequent hydrolysis, and reduction to an alcohol. The tosylate (or halide) of this alcohol can be made, and this electrophile can be used to alkylate **39** to give products with two methylene groups between the ketone and the macrolide group.

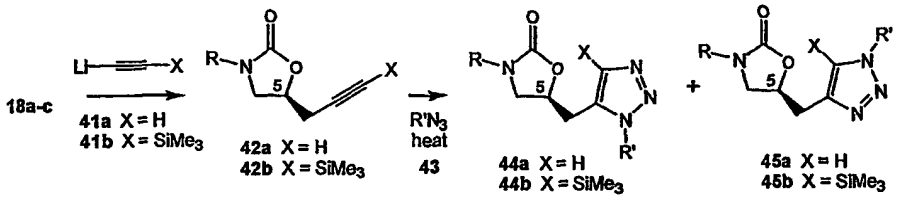
Scheme 4



Scheme 5 illustrates another method to synthesize regioisomeric triazole-linked derivatives of the invention. Carbon-linked triazole derivatives of type **44** and **45** can be produced by first displacing a leaving group, for example, a sulfonate or a halide, from electrophiles **18a-c**, with either lithium acetylide **41a** or lithium trimethylsilylacetylide **41b** to produce alkynes **42a** or **42b**, respectively. The cycloaddition reaction of alkynes **42** with appropriate azides **43** can yield regioisomeric triazoles **44** and **45**. (It will be understood that

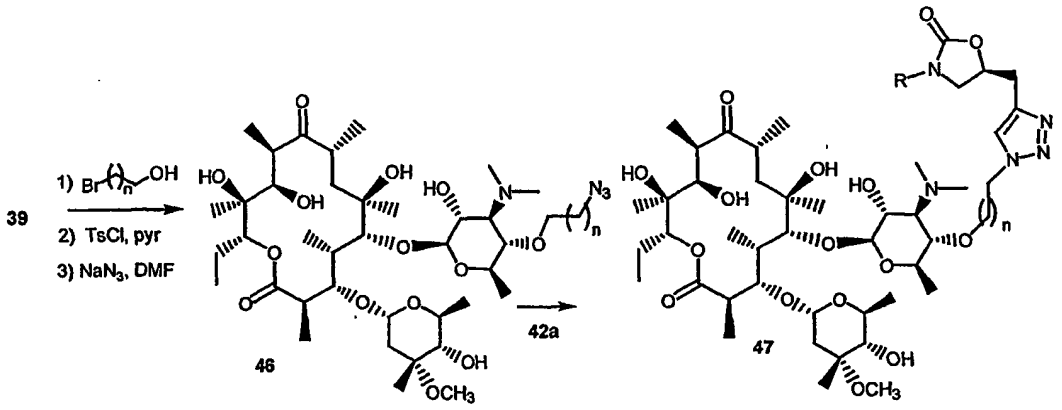
alternative chemical conditions may be employed to produce compounds **44** and **45** such as the use of copper(I)iodide instead of heat.)

Scheme 5



A specific example of the utility of the chemistry expressed in Scheme 5 is shown in Scheme 6. 6-Mycaminosyl-erythromycin derivative **39** (or a suitably protected derivative thereof) can be alkylated with a protected bromoalcohol, and the alcohol function of the product converted to a leaving group such as a tosylate. The tosylate can be displaced with sodium azide to yield azide **46**. Cycloadditon of **46** and alkyne **42a** can produce final targets of type **47**. Alternative alkylsulfonates or halides can be used as the starting material for the synthesis of azide **46** (i.e., different leaving groups). Other mycaminose-containing macrolide entities can be used in place of the 6-mycaminosyl-erythromycin derivative **39** to produce a variety of alternative products.

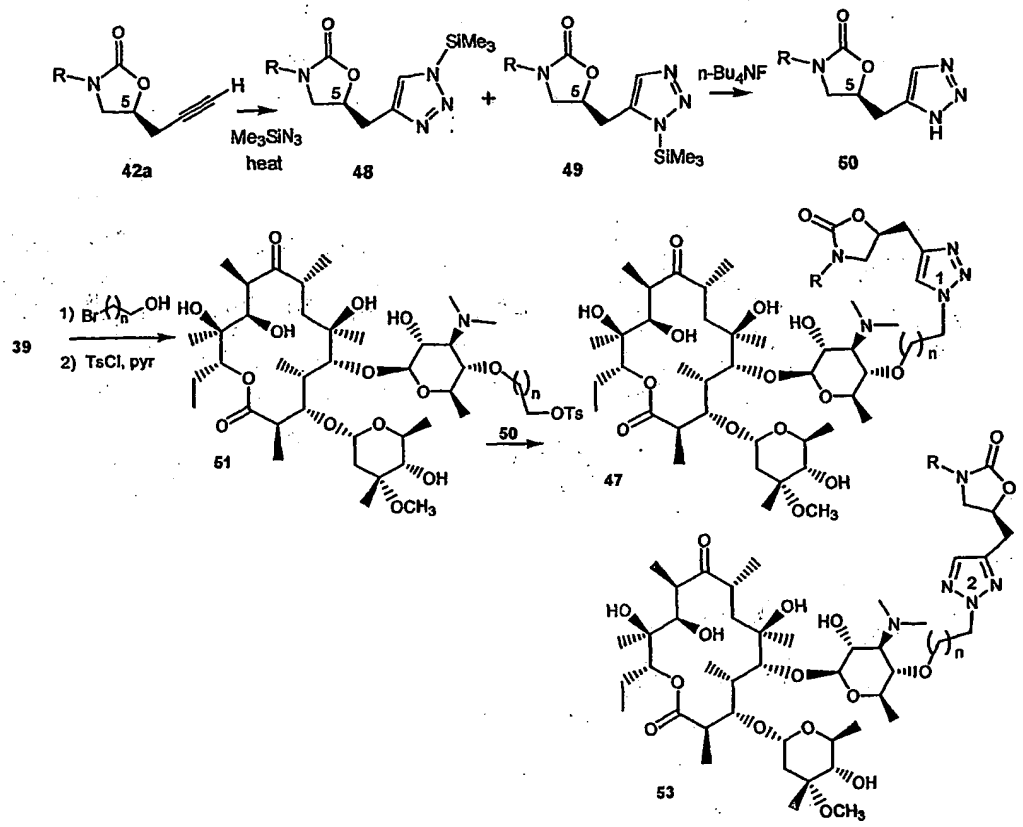
Scheme 6



Another method that can be used to synthesize carbon-linked triazole derivatives of type **47** is illustrated in Scheme 7. Alkyne **42a** can react with trimethylsilylazide (or with sodium azide, ammonium chloride and copper(I)iodide, or other conditions known in the art) to produce two possible regioisomeric products, triazoles **48** and **49**. Either of these (or the mixture) can be desilylated with n-Bu_4NF to produce triazole **50**. Des-methyl erythromycin derivative **39** (or an alternate 4'-hydroxy macrolide derivative) can be converted to tosylate **51** (or another sulfonate or halide electrophile), and then the electrophile can serve to alkylate triazole **50** to produce

either the N-1 substituted triazole **47**, or the N-2 substituted triazole **53**, or a mixture of both. In the event that a mixture is produced, both compounds may be separated from one another. It is contemplated that other macrolides may be transformed by the chemistry of Scheme 7 to produce other compounds of interest.

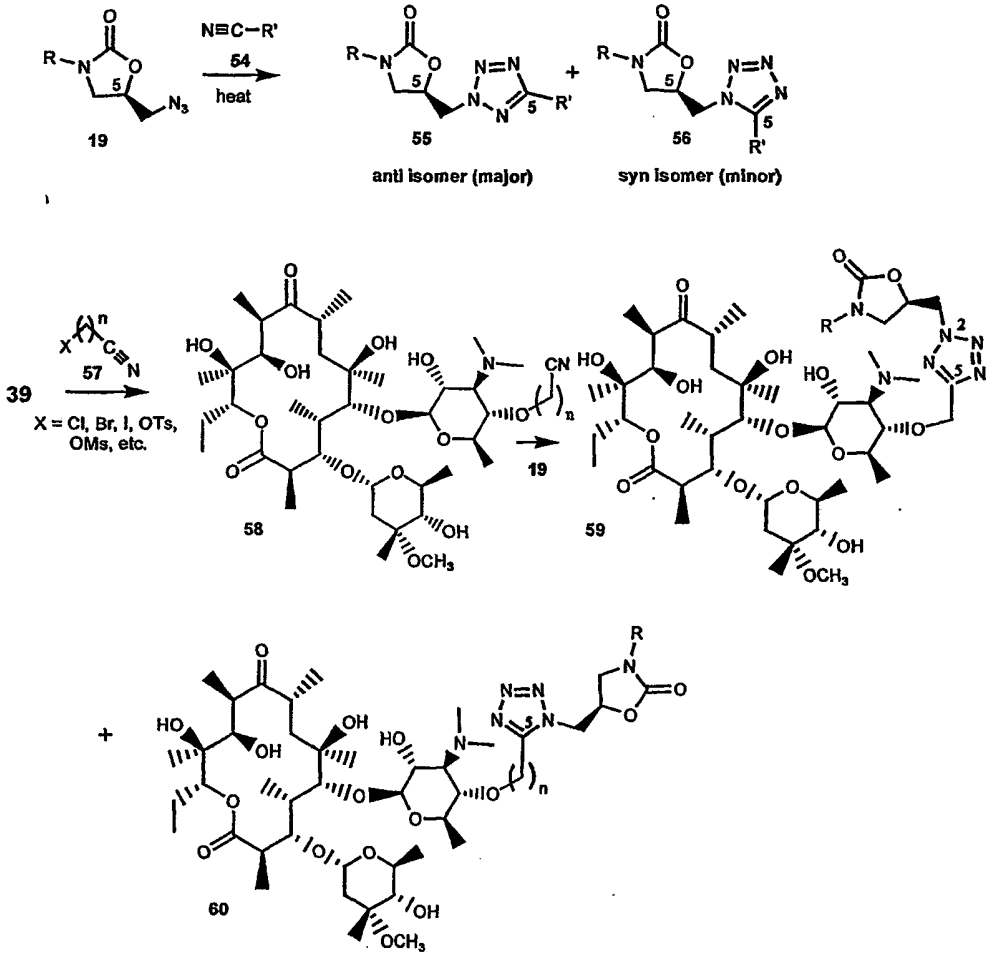
Scheme 7



Scheme 8a illustrates the synthesis of oxazolidinones substituted at C-5 with tetrazolylmethyl derivatives. Azides of type **19** can react with nitriles **54** to produce tetrazoles of type **55** and **56**. In a similar fashion to the chemistry described in Scheme 1, this reaction can yield regioisomeric cycloadducts, where the anti isomer often predominates. As an example, 4'-hydroxy erythromycin **39** can be alkylated with ω-halo or ω-sulfonate nitriles **57** to yield nitriles **58**. These derivatives can react with azides of type **19** to produce target tetrazoles of type **59** and **60**. It is to be understood that the R' group of nitriles **54** may contain the macrolide moiety, or suitable substituted alkyl groups containing an alcohol or protected alcohol that can be converted to a leaving group prior to a final alkylation step with a macrolide. Thus, the tetrazoles **55** and **56** can be produced that have as their R' groups alkyl chains bearing a hydroxy

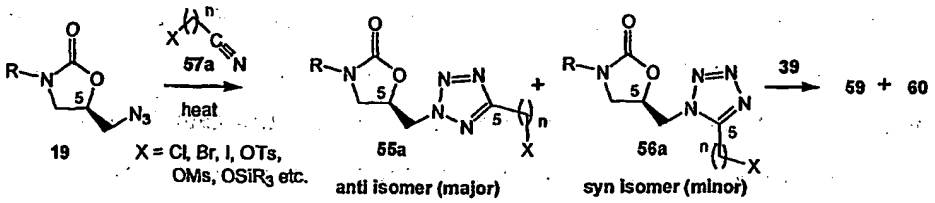
group that can be converted into a sulfonate or halide leaving group prior to alkylation with alcohols similar to **39** to afford products of type **59** and **60**.

Scheme 8a



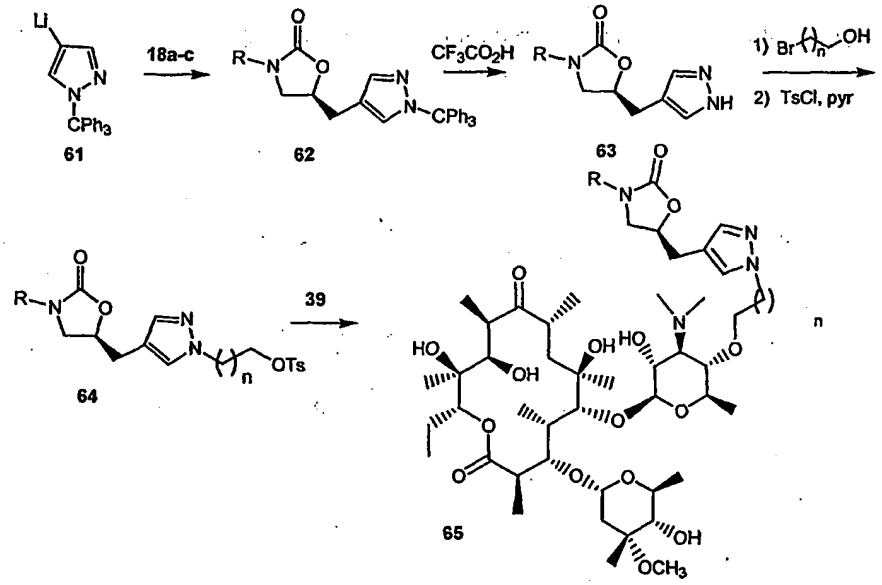
Scheme 8b depicts another strategy to synthesize tetrazoles of type **59** and **60**. Azides **19** may undergo cycloaddition to functionalized nitriles of type **57a** to afford tetrazole intermediates **55a** and **56a**. If **55a** and **56a** contain an appropriate electrophilic group such as a halide or sulfonate, it can react directly with macrolides of type **39** (or a suitably protected derivative thereof) to yield targets of type **59** and **60**. Alternatively, silyloxy-substituted nitriles **57a** may be used during the cycloaddition reaction to afford intermediates of type **55a** and **56a** where X is a silyloxy group. The silylether protecting group may then be removed from **55a** and **56a**, and the resultant alcohol converted to an appropriate electrophile (such as a halide or sulfonate) that would then be suitable for alkylation of macrolides of type **39** to give the desired targets.

Scheme 8b



Scheme 9 illustrates one method of synthesizing pyrazole derivatives of the present invention. Known trityl-protected organolithium derivative **61** (Elguero *et al.* (1997) SYNTHESIS 563) can be alkylated with electrophiles of type **18a-c** to produce pyrazoles of type **62**. Cleavage of the trityl group can be accomplished using a variety of acidic reagents, for example, trifluoroacetic acid (TFA), to produce pyrazole **63**. Alkylation of **63** with a bromoalcohol of appropriate length, followed by tosylation (or alternate sulfonation or halide formation) can produce electrophiles **64**. Alkylation of **39** with **64** produces targets of type **65**. The lithium anions derived from heterocycles such as **61** may optionally be converted to copper (or other metallic) derivatives to facilitate their displacement reactions with sulfonates and halides. These anions may also be allowed to react with suitably protected macrolides, such as the per-silylated derivative of **51**.

Scheme 9

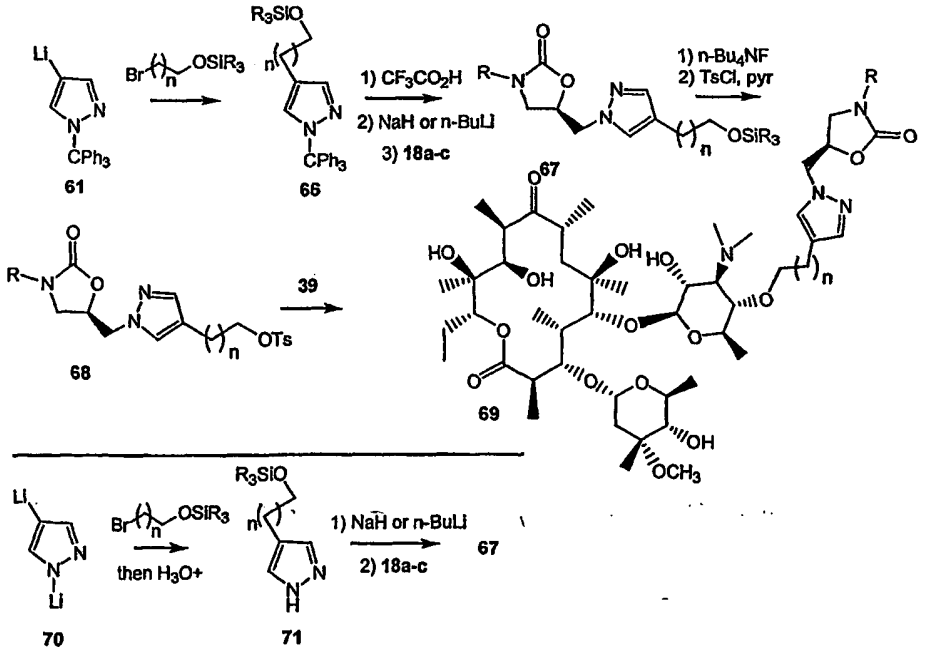


Scheme 10 depicts another method of synthesizing pyrazoles of the present invention. Anions **61** can be alkylated with a bifunctional linker of variable length such as an alkyl halide containing a silyloxy derivative. Alternatively an α,ω dihaloalkyl derivative can be used as the

alkylating agent, or a mixed halo-sulfonate can be employed for this purpose. The resulting substituted pyrazoles **66** can be converted to the free pyrazoles by TFA cleavage of the triphenylmethyl protecting group. The free pyrazoles can undergo direct alkylation with electrophiles **18a-c** in a suitable solvent, for example, dimethylformamide, or can be first converted via deprotonation with a suitable base, for example, sodium hydride or n-butyllithium, to the corresponding anion, if a more reactive nucleophile is required. The resultant pyrazole derivatives **67** can be desilylated and converted to tosylates **68** (if a sulfonate strategy is employed), which can serve as electrophiles for subsequent reaction with macrolide saccharides, for example, **39**, to produce the resultant target **69**.

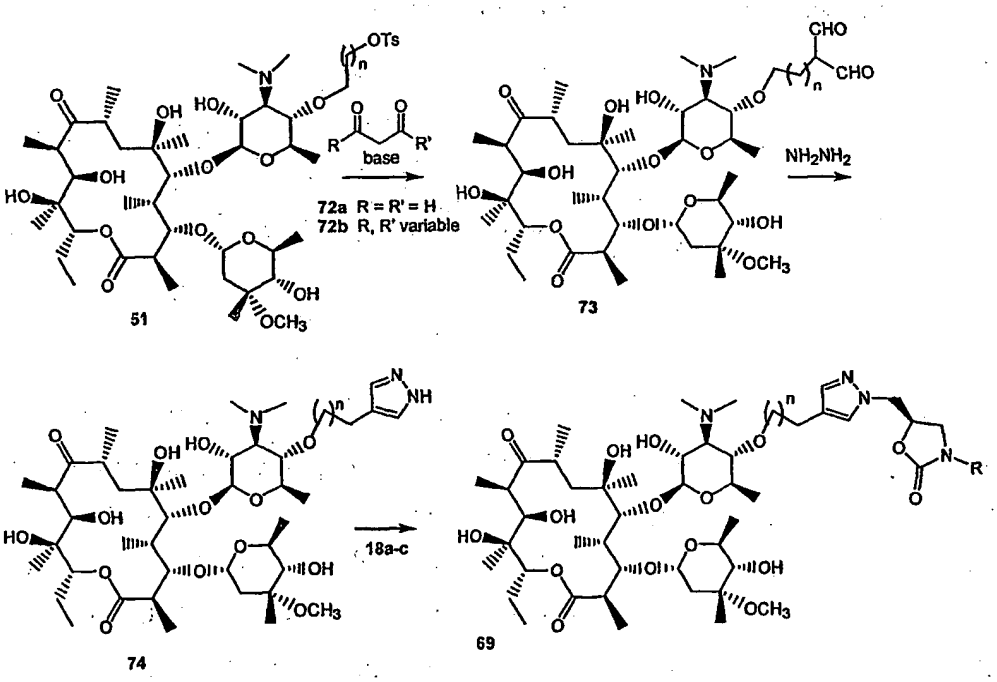
Another approach to intermediates of type **67** can start with alkylation of the known dianion **70** (Hahn *et al.* (1991) J. HETEROCYCLIC CHEM. 28: 1189) with an appropriate bifunctional linker to produce compounds related to pyrazole **71**, which can subsequently be alkylated (with or without prior deprotonation) with electrophiles **18a-c** to produce intermediates **67**. The n = 1 derivatives in this series can be synthesized by trapping compound **61** with DMF to produce the corresponding aldehyde, and then reduction to the alcohol. Alternatively, methoxymethyl (MOM) chloride or bromide can serve as the alkylating reagent for **61**, and hydrolysis of the trityl and MOM groups of the product would yield 4-hydroxymethyl-1,2-pyrazole. The dianion of this pyrazole can be alkylated on nitrogen to produce an alcohol that serves as the precursor for an n = 1 tosylate (or other leaving group).

Scheme 10



Scheme 11 shows an alternate approach for synthesizing pyrazole derivatives of type **69**. Alkylation of the anion of a β-dicarbonyl system with appropriate electrophiles similar to osylate **51** can yield (in the specific example of β-dicarbonyl derivative **72a**) products of type **73**. Treatment of these intermediates with hydrazine can produce pyrazoles of type **74**. Direct alkylation of **74** with electrophiles **18a-c** can proceed to produce targets **69**. Alternatively, the hydroxyl residues of **74** (and other sensitive functional groups of other macrolide derivatives such as intermediates **39** and **51**) can be protected with suitable protecting groups (such as those highlighted in Greene, T.W. and Wuts, P.G.M. *supra*), and the hydrogen atom on the nitrogen atom of the pyrazole derivative deprotonated with a suitable base, for example, sodium hydride or n-butyllithium. The resulting anion can then be alkylated with electrophiles **18a-c**, and the resulting product deprotected to produce targets **69**. The use of protecting groups well known to those skilled in the art for the macrolide portions of these intermediates may be required for many of the subsequent reactions shown in the schemes below that involve heteroaryl anion alkylations.

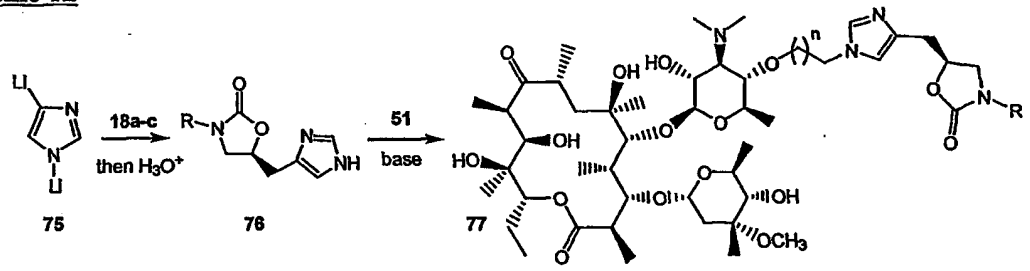
Scheme 11



Scheme 12 exemplifies a synthesis of imidazoles of the present invention. The known dianion **75** (Katritzky *et al.* (1989) J. CHEM. SOC. PERKIN TRANS. 1: 1139) can react with electrophiles **18a-c** to produce after protic work-up imidazoles of type **76**. Direct alkylation of **76** by heating with electrophiles related to **51** in an appropriate organic solvent can yield 1,4-

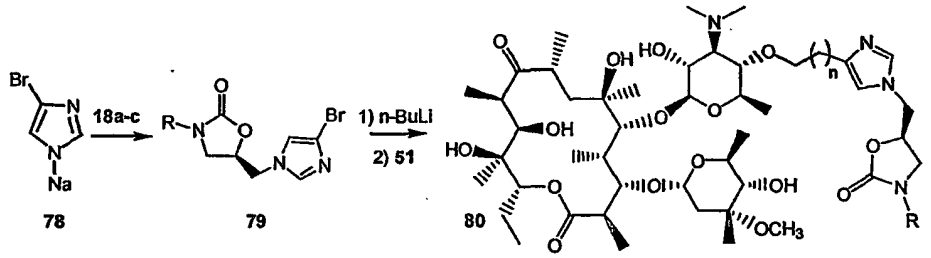
disubstituted imidazoles **77**. Alternatively, the imidazole anion formed via deprotonation of the imidazole hydrogen atom of **76** with a suitable base and then alkylation with **51** can also produce **77**.

Scheme 12



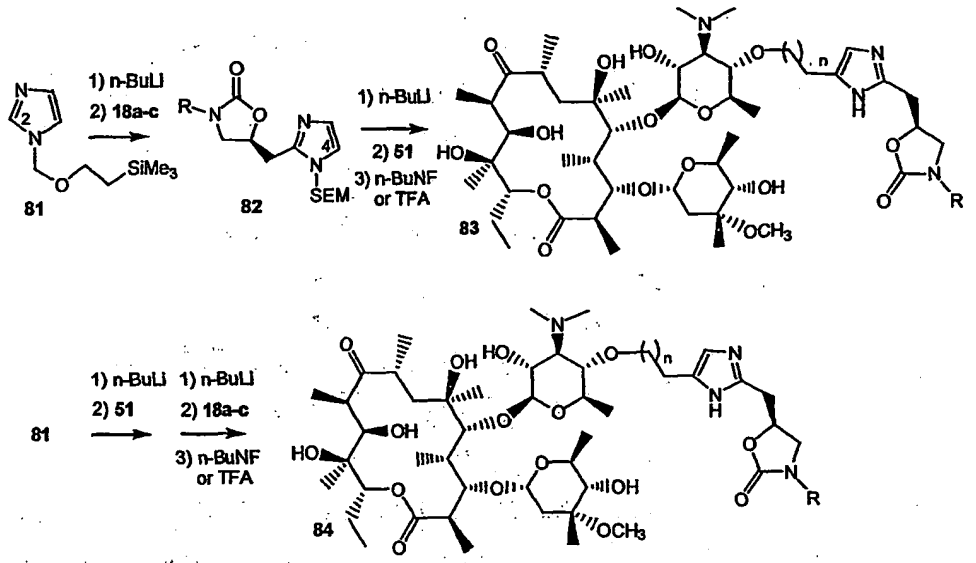
Scheme 13 illustrates another synthesis of imidazoles of the present invention. 4-Bromoimidazole can be deprotonated using, for example, sodium hydride or lithium diisopropylamide, or another suitable organic base, to give anion **78** (or the corresponding lithio derivative). Alkylation of **78** with **18a-c** can yield bromoimidazole **79** which can then be subjected to metal-halogen exchange and alkylated with **51** (or a suitably protected derivative of **51**) to produce isomeric 1,4-disubstituted imidazoles **80**.

Scheme 13



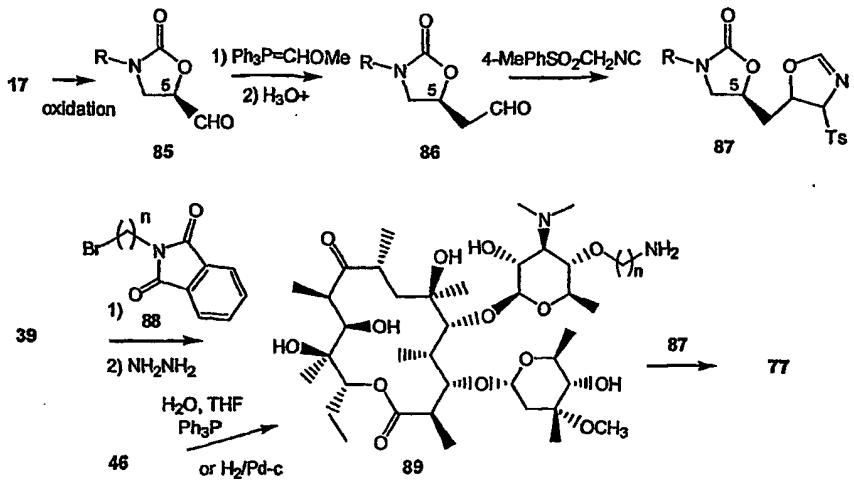
Scheme 14 depicts chemistry suitable for the synthesis of other target imidazole derivatives. The silylethoxymethyl (SEM) protected imidazole **81** can be lithiated at C-2 (Shapiro *et al.* (1995) HETEROCYCLES 41: 215) and can react with electrophiles **18a-c** to produce imidazole intermediates **82**. Lithiation of imidazole intermediates **82** at C-4 of the imidazole, followed by alkylation with electrophiles of type **51** (or a suitably protected version such as the per-silylated derivative), and then deprotection of the SEM can produce imidazoles **83**.

Scheme 14



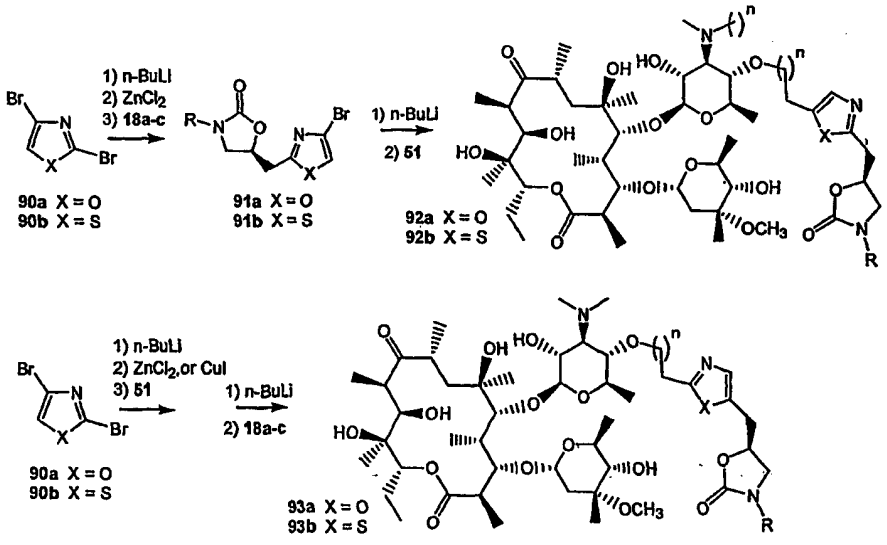
Scheme 15 shows how tosylmethyl isocyanide can be used to make imidazoles of the present invention (Vanelle *et al.* (2000) EUR. J. MED. CHEM. 35: 157; Horne *et al.* (1994) HETEROCYCLES 39: 139). Alcohols **17** can be oxidized to produce aldehydes **85** using an appropriate agent such as the Dess-Martin periodinane, or oxalyl chloride/dimethylsulfoxide/ triethylamine (Swern oxidation). A variety of chromium complexes can also be used for this oxidation, including, for example, pyridinium dichromate (PDC), pyridinium chlorochromate (PCC), chromium trioxide, and tetrapropylammonium perruthenate. Wittig homologation of **85** can provide aldehyde **86**, which can then be converted by tosylmethyl isocyanide to produce intermediate **87**. The reaction of **87** with **89** (formed via alkylation of alcohols **39** with bromoalkyl phthalimides **88** (followed by hydrazine cleavage) or reduction of azides **46**) can produce imidazoles **77**.

Scheme 15



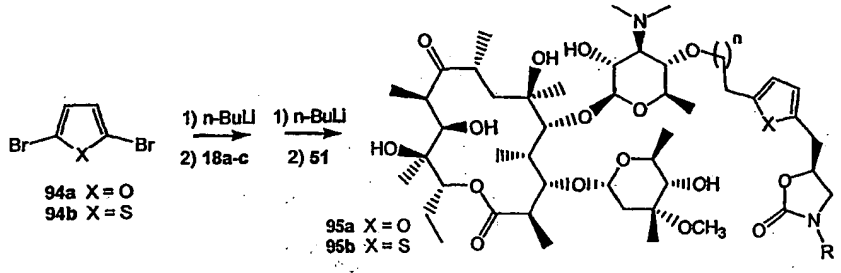
Scheme 16 delineates how 1,3 thiazole and 1,3 oxazole derivatives of the present nvention can be synthesized. Known dibromo thiazoles and oxazoles **90a** and **90b** can be selectively metallated at C-2 and alkylated with electrophiles **18a-c** to produce intermediates **91a** and **91b** (Pinkerton *et al.* (1972) J. HETEROCYCLIC CHEMISTRY 9: 67). Transmetallation with zinc chloride can be employed in the case of the oxazole anion if the anion displays any tendency to ring open prior to its reaction with certain electrophiles. The bromo azoles **91** can be metallated to form the corresponding anion which can undergo alkylation with sulfonates **51** (or the related halides) to produce the final targets **92**. Reordering of the sequence of electrophiles in this process permits access to the isomeric thiazoles and oxazoles **93**.

Scheme 16



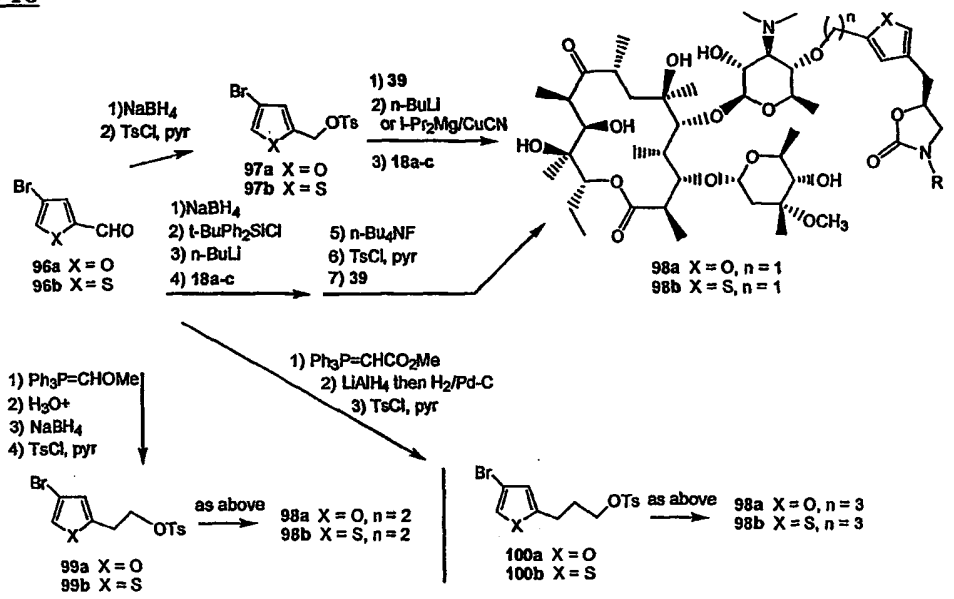
Scheme 17 shows the synthesis of 2,5 disubstituted furan and thiophene derivatives of the invention. Commercially available dibromofuran **94a** and dibromothiophene **94b** can be monolithiated (Cherioux *et al.* (2001) ADVANCED FUNCTIONAL MATERIALS 11: 305) and alkylated with electrophiles **18a-c**. The monobromo intermediates obtained from this reaction can be lithiated again and then alkylated with electrophiles of type **51** (or a protected version of **51**) to produce the final targets **95**.

Scheme 17



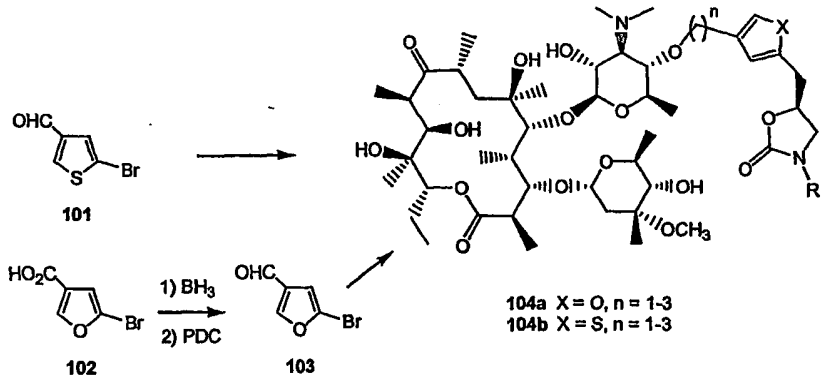
Scheme 18 depicts the synthesis of 2,4 disubstituted furan and thiophene derivatives of the invention. Commercially available furan aldehyde **96a**, and the known thiophene aldehyde **96b**, can be reduced to the corresponding alcohols and the resulting alcohols converted to a leaving group such as tosylates **97**. Alternate sulfonates and halides can be synthesized and used in this fashion. The tosylates **97** can alkylate alcohol **39** (or a protected version thereof), and the heteroaryl bromide can be converted to a suitable organometallic agent (by reagents such as n-BuLi, or i-Pr_2Mg/CuCN). This intermediate organometallic agent can be alkylated with electrophiles **18a-c** to produce targets of type **98** where n = 1. As the scheme shows, a reordering of steps can be employed involving reduction, silylation, lithiation and then initial alkylation with **18a-c**. Desilylation of the alkylation product, followed by tosylation of the alcohol, provides an intermediate that can then be alkylated with alcohol **39** to produce targets **98**. Simple homologation protocols, using the reagents depicted in Scheme 18 or others known to those skilled in the art, can convert the aldehydes **96** to longer chain tosylates such as **99** and **100**. The use of these tosylates in the alkylation with **39**, and subsequent metal-halogen exchange and alkylation with **18a-c**, can yield compounds of type **98** where n = 2 and 3. It will be appreciated that longer chain tosylates can be produced using chemistries similar to that depicted in Scheme 18, and that other bifunctional linkers can be used to produce compounds of type **98**.

Scheme 18



Chemistries similar to that employed above in Scheme 18 can convert known thiophene aldehyde **101** (Eras *et al.* (1984) J. HETEROCYCLIC CHEM. 21: 215) to produce products of type **104** (Scheme 19). The known acid **102** (Wang *et al.* (1996) TETRAHEDRON LETT. 52: 12137) can be converted to aldehyde **103** by reduction with, for example, borane or lithium aluminum hydride, followed by oxidation of the resultant hydroxymethyl intermediate with, for example, PDC, PCC, or another suitable reagent. Aldehyde **103** can then be converted to produce compounds of type **104**.

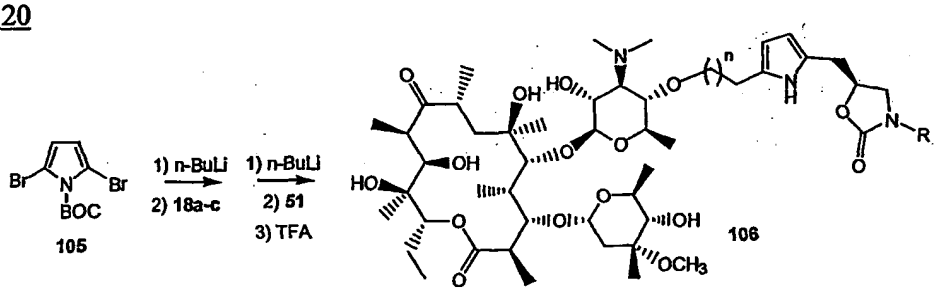
Scheme 19



Scheme 20 illustrates the synthesis of 2,5 disubstituted pyrroles of the invention. The BOC-protected dibromopyrrole **105** can be lithiated and alkylated sequentially (Chen *et al.* (1987) TETRAHEDRON LETT. 28: 6025; Chen *et al.* (1992) ORG. SYNTH. 70: 151; and Martina *et al.* (1991) SYNTHESIS 613), and allowed to react with electrophiles **18a-c** and **51** (or a

suitably protected analogue of 51) to produce, after final BOC deprotection with TFA, disubstituted pyrroles of type **106**.

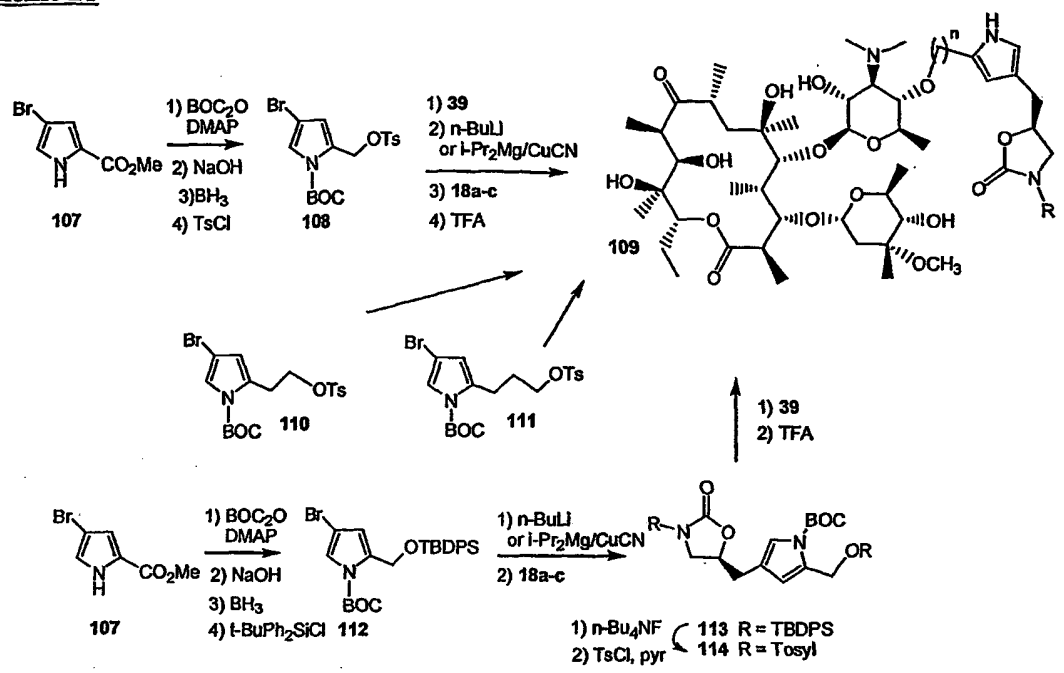
Scheme 20



Scheme 21 shows the synthesis of 2,4 disubstituted pyrroles of the invention. Commercially available pyrrole ester **107** can be protected with a suitable protecting group, for example, the BOC group, and the ester function hydrolyzed to the corresponding acid. The resulting acid can then be reduced to the alcohol using, for example, borane to yield an alcohol that can be converted to tosylate **108**. Alcohol **39** (or a suitably protected version of **39**, formed for example by silylation of the other hydroxyl groups with bis-trimethylsilylacetamide or another silylating reagent) can be alkylated with tosylate **108** to produce an intermediate bromopyrrole. The bromopyrrole can then be converted to an organometallic reagent that can then react with electrophiles **18a-c**. The resulting product can then be deprotected with TFA to produce pyrroles **109**. The alcohol formed after borane reduction of the acid derived from **107** can then be homologated to tosylates **110** and **111** by chemistries similar to that shown below in Scheme 23. The use of these tosylates in the alkylation strategy can produce target pyrroles of type **109** where n = 2 and 3.

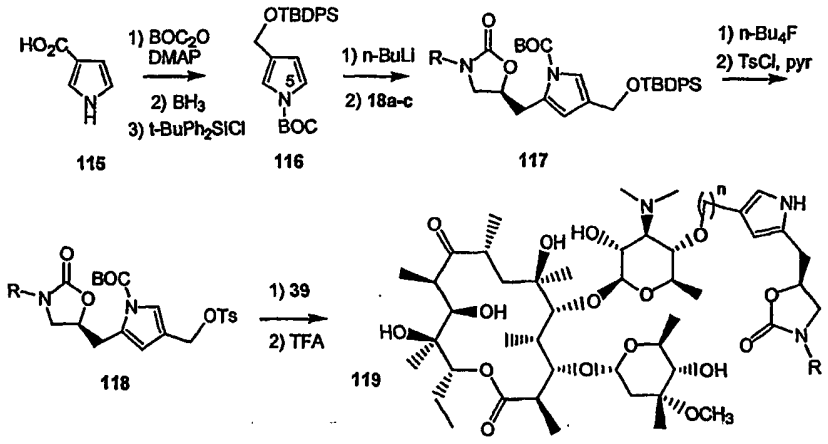
An alternative approach is to protect the alcohol functions prior to tosylation, and perform the alkylation of the organometallic derived from the halopyrrole with **18a-c** first. For example, silyloxy derivative **112** can be produced from **107**, and the organometallic derivative derived from it alkylated with **18a-c** to yield silyl ethers **113**. Subsequent desilylation and conversion to tosylates **114** provides an electrophile that can be used in the alkylation reaction with **39**. A final BOC cleavage can then give pyrroles **109**. It is understood that the alcohol precursor of **112** can be homologated, using chemistries similar to that shown below in Scheme 23 and other schemes) to other alkanols that can be tosylated for further reactions with alcohol **39** (or related macrolides). Furthermore, the alcohol derived from silyl cleavage of **113** can serve as the starting material for this type of homologation efforts to produce the alkyl tosylates (or halides) required for making targets **109** where n is variable.

Scheme 21



Scheme 22 shows the synthesis of isomeric 2,4 disubstituted pyrroles of the invention. Commercially available pyrrole acid **115** can be protected as the BOC derivative, and the acid function reduced to an alcohol, which can then be protected to produce the silyl ether **116**. Deprotonation of **116** with n-butyllithium can occur at the 5 position of the pyrrole ring, and this anion (or that derived from transmetallation with an appropriate metal) can be alkylated with electrophiles **18a-c** to produce pyrrole **117**. Desilylation of **117**, followed by tosylation, alkylation with **39**, and TFA deprotection of the BOC group can yield pyrroles **119**.

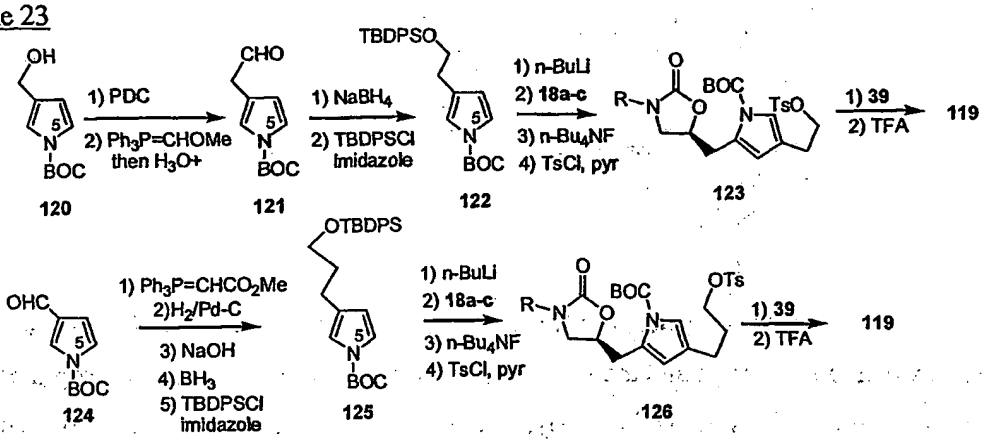
Scheme 22



Scheme 23 illustrates the synthesis of longer chain tosylates of type **123** and **126** used to alkylate alcohols of type **39** to produce pyrroles **119**. The alcohol **120** derived from protection

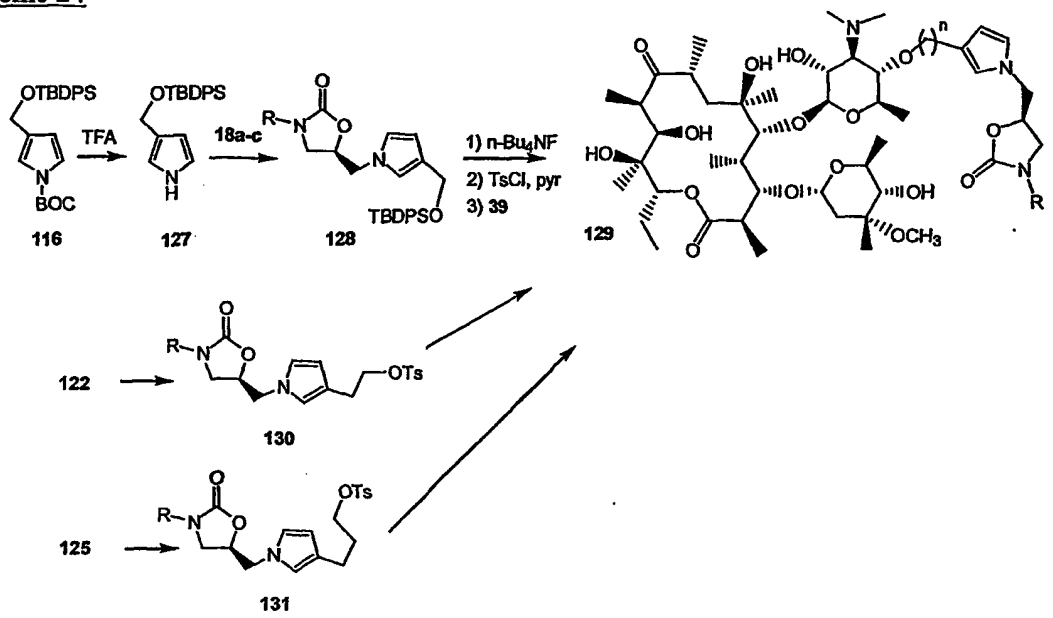
of 115 followed by borane reduction can be oxidized to aldehyde **124**. The Wittig reaction of aldehyde **124** with methoxymethyl triphenylphosphorane is followed by an acid hydrolysis step to produce the homologated aldehyde **121**. Reduction and silyl protection can yield **122**, which can then be deprotonated, alkylated and then converted to tosylate **123**. Aldehyde **124** can undergo a Wittig reaction with carbomethoxymethyl triphenylphosphorane. The Wittig product then is reduced to an alkanol that can then be silylated to produce **125**. Conversion of **125** to pyrroles **119** can then occur using the same chemistry employed to provide **119** from **122**.

Scheme 23



Scheme 24 shows the synthesis of 1,3 disubstituted pyrroles of the present invention. The BOC group of **116** can be cleaved to produce free pyrrole **127**. Alkylation of **127** (in a suitable organic solvent such as DMF) with **18a-c** can produce intermediate **128**. The dianion of 3-hydroxymethylpyrrole can also be suitable for alkylation with **18a-c** to produce the free hydroxy derivative of silyl ether **128**. Conversion of the siloxy group to the corresponding tosylate, followed by alkylation with alcohols of type **39** can generate the target N-substituted pyrroles **129** (where n = 1). In a similar fashion, the BOC pyrroles **122** and **125** can be converted to the tosylates **130** and **131**. These tosylates can be used to produce pyrroles of type **129** (where n = 2 and 3). It is understood that longer chain alkyl tosylates (and halides) can be produced that can undergo this chemistry to produce pyrroles **129** where n is > 3.

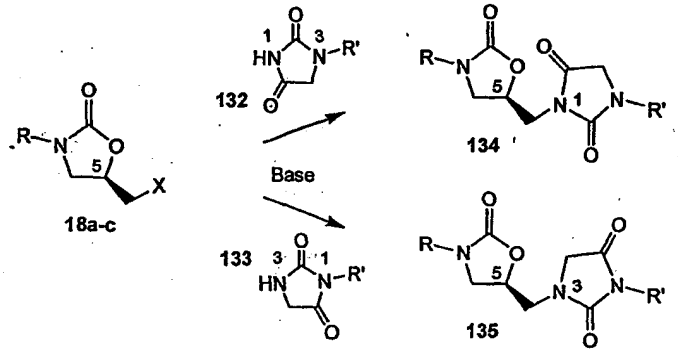
Scheme 24



Scheme 25 illustrates the use of hydantoin-like groups as the 5-membered heterocyclic linker between the G groups and the R_1 moieties of the present invention. Electrophiles of type **18a-c** can alkylate anions derived from hydantoins to produce compounds of the present invention. For example, 3-substituted hydantoins of type **132** can be purchased and treated with an appropriate base to generate the corresponding imide anion. The resulting anions can be alkylated with electrophiles similar (but not limited) to intermediates **18a-c** to produce hydantoin derivatives **134**. Alternatively, 1-substituted hydantoins of type **133** can be purchased or prepared, and treated with base and electrophile to yield isomeric hydantoin derivatives **135**. It is understood that such hydantoins can have, for example, at optional locations, thiocarbonyl functionalities in place of the illustrated carbonyl groups. Such compounds can be prepared by treatment of the oxy-hydantoins with Lawesson's reagent, elemental sulfur, phosphorus pentasulfide, and other reagents commonly used in the art to perform this transformation.

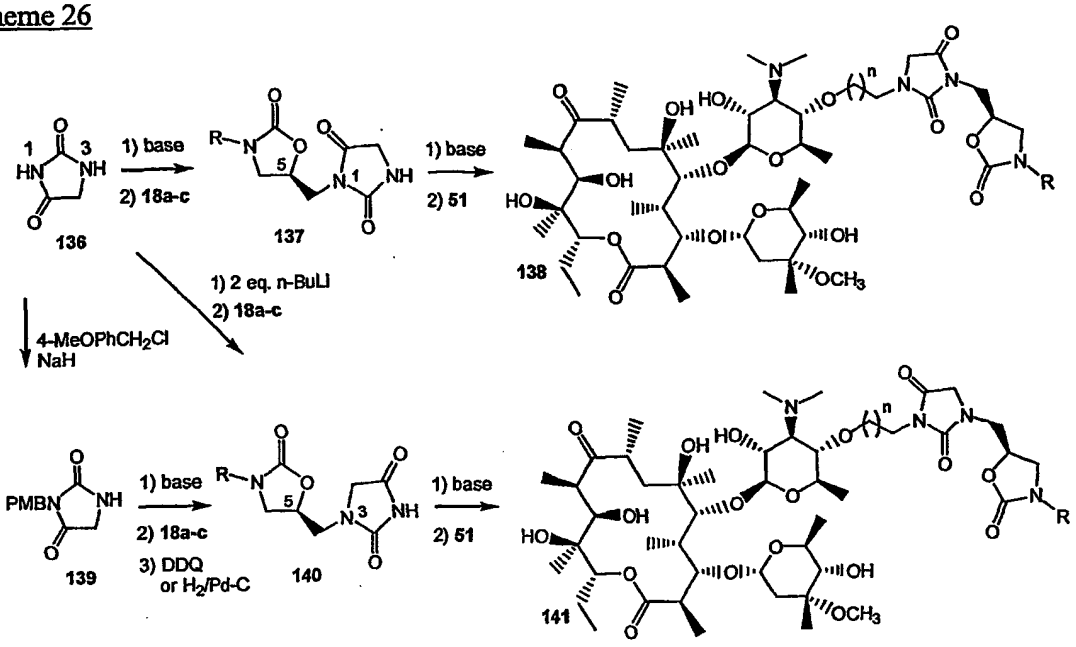
Alternatively, such thiohydantoins can be synthesized selectively by sequential synthetic steps known in the art. The R' group of **132** and **133** may represent a protecting group function, for example, benzyl, alkoxybenzyl, benzyloxycarbonyl, t-butoxycarbonyl, that is compatible with the alkylation step. Such a protecting group can subsequently be removed from products **134** and **135**, yielding products where the R' group is a hydrogen atom. These intermediates can be used to produce various target molecules by their treatment with base and then subsequent exposure to appropriate electrophiles.

Scheme 25



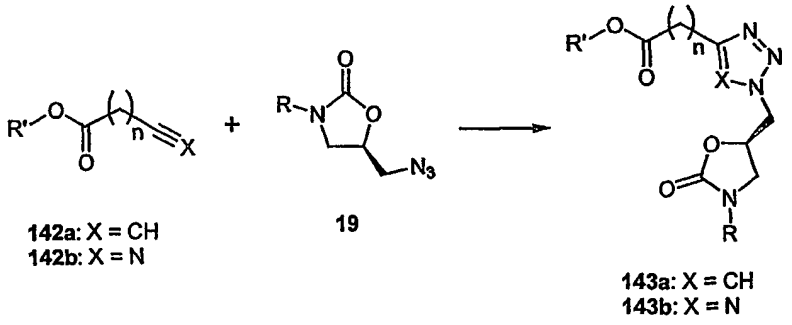
A more specific example of the synthesis of hydantoin derivatives of the present invention is depicted in Scheme 26. Hydantoin **136** can be treated with a mild organic base, for example, sodium hydride, potassium tertiary-butoxide, cesium, sodium, or potassium carbonate, to produce the N-1 substituted intermediate **137**. Deprotonation of **137** with a base, for example, sodium hydride, n-butyllithium, lithium bis-trimethylsilylamide or lithium diisopropylamide, followed by alkylation with **51** (or a suitably protected derivative of **51**) can yield hydantoin targets of type **138**. The isomeric hydantoin derivatives of type **141** can be synthesized from **136** by initial p-methoxybenzyl (PMB) protection of the N-1 position, followed by alkylation at N-3 with **18a-c** and subsequent deprotection of the PMB group with either 2,3-dichloro-3,4-dicyano-benzoquinone (DDQ) or hydrogenation will yield hydantoin intermediates **140**. Subsequent alkylation of **140** with **51** can give compounds **141**. Another route to produce intermediates **140** is by formation of the dianion of hydantoin **136**. One equivalent of a weak base can deprotonate the N-1 position of **136**. The addition of another equivalent of a strong base, for example, n-butyllithium, to the initial anion can deprotonate it again, this time at N-3. Alkylation can occur at the more reactive position (N-3) to again produce hydantoins **140**.

Scheme 26



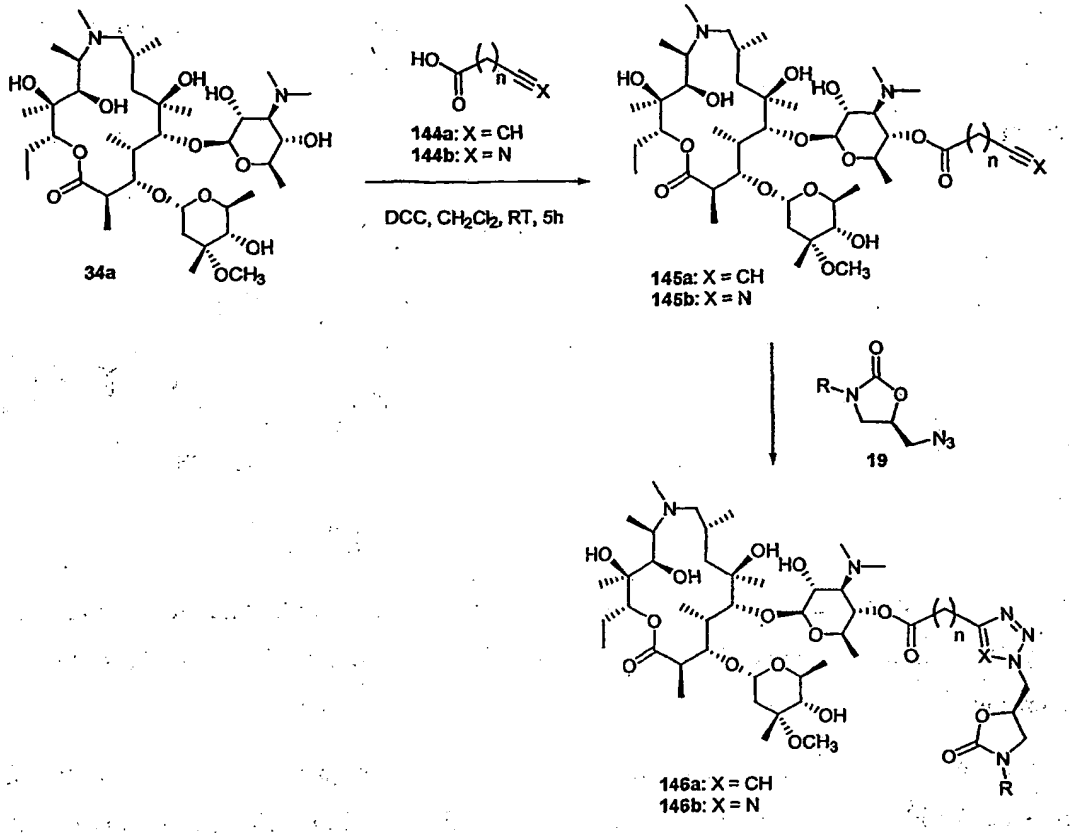
Compounds of the present invention containing an ester moiety linking the 5-membered heterocyclic ring to the macrolide can be prepared. Scheme 27 illustratates how alkynyl ester **142a** or cyano ester **142b** can be treated with azide **19** to yield the corresponding triazole **143a** or tetrazole **143b**, respecitvely.

Scheme 27



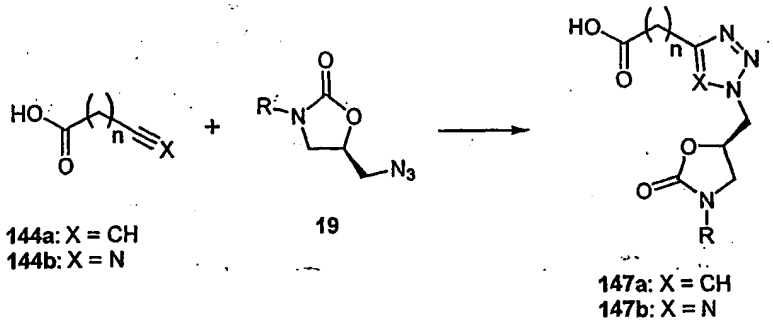
The chemistry illustrated in Scheme 27 can be applied to macrolide systems containing alknynyl or cyano esters, as illustrated in Scheme 28. Here, 6-O-mycaminosyl azithromycin **34a** is treated with alkynyl carboxylic acid **144a** or cyano carboxylic acid **144b** under mild esterification conditions (using a coupling agent such as DCC, EDC, HOBt, etc.) to yield the alkynyl ester **145a** or the cyano ester **145b**. These esters are then treated with azide **19** to yield via a cycloaddition reaction the triazole **146a** or the tetrazole **146b**.

Scheme 28



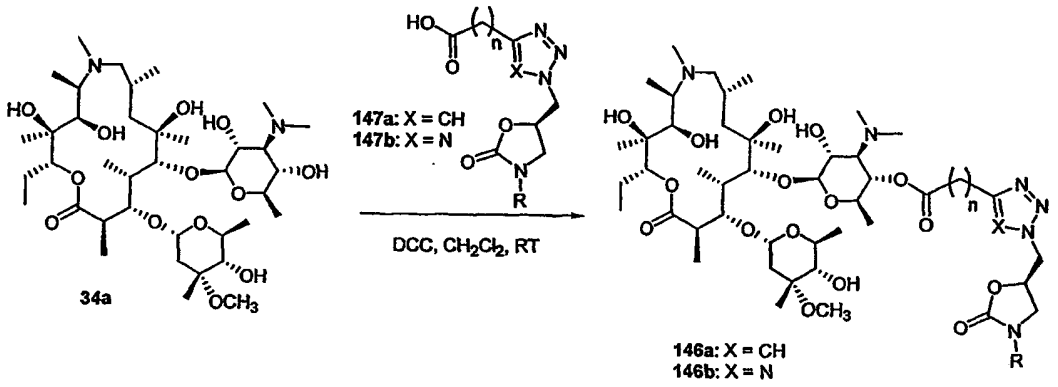
Alternatively, compounds of the present invention containing an ester moiety linking the 5-membered heterocyclic ring to the macrolide can be prepared by first forming the cycloaddition product from an alkynyl or cyano carboxylic acid, and subsequently esterifying with a macrolide. Scheme 29 illustratates how an alkynyl carboxylic acid **144a** or a cyano carboxylic acid **144b** can be treated with azide **19** to yield the corresponding triazole acid **147a** or tetrazole acid **147b**, respecitvely.

Scheme 29



Scheme 29 illustrates the reaction of 6-O-mycaminosyl azithromycin **34a** with carboxylic acid **147a** or **147b** under mild esterification conditions (using a coupling agent such as DCC, EDC, HOBt, etc.) to yield the final product **146a** or **146b**.

Scheme 30



In addition to the foregoing, compounds disclosed in the following publications, patents and patent applications are suitable intermediates for preparation of the compounds of this invention:

Tucker, J.A. *et al., J. Med. Chem.*, **1998**, *41*, 3727; Gregory, W.A. *et al., J. Med. Chem.*, 1990, *33*, 2569; Genin, M.J. *et al., J. Med. Chem.*, **1998**, *41*, 5144; Brickner, S.J. *et al., J. Med. Chem.*, **1996**, *39*, 673. Barbachyn, M.R. *et al., J. Med. Chem.*, **1996**, *39*, 680; Barbachyn, M.R. *et al., Bioorg. Med. Chem. Lett.*, **1996**, *6*, 1003; Barbachyn, M.R. *et al., Bioorg. Med. Chem. Lett.*, **1996**, *6*, 1009; Grega, K.C. *et al., J. Org. Chem.*, **1995**, *60*, 5255; Park, C.-H. *et al., J. Med. Chem.*, **1992**, *35*, 1156; Yu, D. *et al., Bioorg. Med. Chem. Lett.*, **2002**, *12*, 857; Weidner-Wells, M.A. *et al., Bioorg. Med. Chem.*, **2002**, *10*, 2345; and Cacchi, S. *et al., Org. Lett.*, **2001**, 3, 2539. U.S. Patent Nos. 4,801,600; 4,948, 801; 5,736,545; 6,362,189; 5,523,403; 4,461,773; 5,365,751; 6,124,334; 6,239,152; 5,981,528; 6,194,441; 6,147,197; 6,034,069; 4,990,602; 5,124,269; and 6,271,383. U.S. Patent Application Nos. 2001/0046992, PCT Application and publications WO96/15130; WO95/14684; WO 99/28317; WO 98/01447; WO 98/01446; WO 97/31917; WO 97/27188; WO 97/10223; WO 97/09328; WO 01/46164; WO 01/09107; WO 00/73301; WO 00/21960; WO 01/81350; WO 97/30995; WO 99/10342; WO 99/10343; WO 99/64416; WO 00/232917; and WO 99/64417, European Patent Nos. EP 0312000 B1; EP 0359418 A1; EP 00345627; EP 1132392; and EP 0738726 A1.

4. Characterization of Compounds of the Invention

Compounds designed, selected and/or optimized by methods described herein, once produced, may be characterized using a variety of assays known to those skilled in the art to determine whether the compounds have biological activity. For example, the molecules may be characterized by conventional assays, including but not limited to those assays described below, to determine whether they have a predicted activity, binding activity and/or binding specificity.

Furthermore, high-throughput screening may be used to speed up analysis using such assays. As a result, it may be possible to rapidly screen the molecules described herein for activity, for example, as anti-cancer, anti-bacterial, anti-fungal, anti-parasitic or anti-viral agents. Also, it may be possible to assay how the compounds interact with a ribosome or ribosomal subunit and/or are effective as modulators (for example, inhibitors) of protein synthesis using techniques known in the art. General methodologies for performing high-throughput screening are described, for example, in Devlin (1998) High Throughput Screening, Marcel Dekker; and U.S. Patent No. 5,763,263. High-throughput assays can use one or more different assay techniques including, but not limited to, those described below.

(1) *Surface Binding Studies.* A variety of binding assays may be useful in screening new molecules for their binding activity. One approach includes surface plasmon resonance (SPR) that can be used to evaluate the binding properties of molecules of interest with respect to a ribosome, ribosomal subunit or a fragment thereof.

SPR methodologies measure the interaction between two or more macromolecules in real-time through the generation of a quantum-mechanical surface plasmon. One device, (BIAcore Biosensor RTM from Pharmacia Biosensor, Piscatawy, N.J.) provides a focused beam of polychromatic light to the interface between a gold film (provided as a disposable biosensor "chip") and a buffer compartment that can be regulated by the user. A 100 nm thick "hydrogel" composed of carboxylated dextran that provides a matrix for the covalent immobilization of analytes of interest is attached to the gold film. When the focused light interacts with the free electron cloud of the gold film, plasmon resonance is enhanced. The resulting reflected light is spectrally depleted in wavelengths that optimally evolved the resonance. By separating the reflected polychromatic light into its component wavelengths (by means of a prism), and determining the frequencies that are depleted, the BIAcore establishes an optical interface which accurately reports the behavior of the generated surface plasmon resonance. When designed as above, the plasmon resonance (and thus the depletion spectrum) is sensitive to mass in the

evanescent field (which corresponds roughly to the thickness of the hydrogel). If one component of an interacting pair is immobilized to the hydrogel, and the interacting partner is provided through the buffer compartment, the interaction between the two components can be measured in real time based on the accumulation of mass in the evanescent field and its corresponding effects of the plasmon resonance as measured by the depletion spectrum. This system permits rapid and sensitive real-time measurement of the molecular interactions without the need to label either component.

(2) *Fluorescence Polarization.* Fluorescence polarization (FP) is a measurement technique that can readily be applied to protein-protein, protein-ligand, or RNA-ligand interactions in order to derive IC_{50}s and Kds of the association reaction between two molecules. In this technique one of the molecules of interest is conjugated with a fluorophore. This is generally the smaller molecule in the system (in this case, the compound of interest). The sample mixture, containing both the ligand-probe conjugate and the ribosome, ribosomal subunit or fragment thereof, is excited with vertically polarized light. Light is absorbed by the probe fluorophores, and re-emitted a short time later. The degree of polarization of the emitted light is measured. Polarization of the emitted light is dependent on several factors, but most importantly on viscosity of the solution and on the apparent molecular weight of the fluorophore. With proper controls, changes in the degree of polarization of the emitted light depends only on changes in the apparent molecular weight of the fluorophore, which in-turn depends on whether the probe-ligand conjugate is free in solution, or is bound to a receptor. Binding assays based on FP have a number of important advantages, including the measurement of IC_{50}s and Kds under true homogenous equilibrium conditions, speed of analysis and amenity to automation, and ability to screen in cloudy suspensions and colored solutions.

(3) *Protein Synthesis.* It is contemplated that, in addition to characterization by the foregoing biochemical assays, the compound of interest may also be characterized as a modulator (for example, an inhibitor of protein synthesis) of the functional activity of the ribosome or ribosomal subunit.

Furthermore, more specific protein synthesis inhibition assays may be performed by administering the compound to a whole organism, tissue, organ, organelle, cell, a cellular or subcellular extract, or a purified ribosome preparation and observing its pharmacological and inhibitory properties by determining, for example, its inhibition constant (IC_{50}) for inhibiting protein synthesis. Incorporation of ^{3}H leucine or ^{35}S methionine, or similar experiments can be performed to investigate protein synthesis activity. A change in the amount or the rate of

protein synthesis in the cell in the presence of a molecule of interest indicates that the molecule is a modulator of protein synthesis. A decrease in the rate or the amount of protein synthesis indicates that the molecule is a inhibitor of protein synthesis.

Furthermore, the compounds may be assayed for anti-proliferative or anti-infective properties on a cellular level. For example, where the target organism is a microorganism, the activity of compounds of interest may be assayed by growing the microorganisms of interest in media either containing or lacking the compound. Growth inhibition may be indicative that the molecule may be acting as a protein synthesis inhibitor. More specifically, the activity of the compounds of interest against bacterial pathogens may be demonstrated by the ability of the compound to inhibit growth of defined strains of human pathogens. For this purpose, a panel of bacterial strains can be assembled to include a variety of target pathogenic species, some containing resistance mechanisms that have been characterized. Use of such a panel of organisms permits the determination of structure-activity relationships not only in regards to potency and spectrum, but also with a view to obviating resistance mechanisms. The assays may be performed in microtiter trays according to conventional methodologies as published by The National Committee for Clinical Laboratory Standards (NCCLS) guidelines (NCCLS. M7-A5-Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Fifth Edition. NCCLS Document M100-S12/M7 (ISBN 1-56238-394-9)).

5. Formulation and Administration

The compounds of the invention may be useful in the prevention or treatment of a variety of human or other animal disorders, including for example, bacterial infection, fungal infections, viral infections, parasitic diseases, and cancer. It is contemplated that, once identified, the active molecules of the invention may be incorporated into any suitable carrier prior to use. The dose of active molecule, mode of administration and use of suitable carrier will depend upon the intended recipient and target organism. The formulations, both for veterinary and for human medical use, of compounds according to the present invention typically include such compounds in association with a pharmaceutically acceptable carrier.

The carrier(s) should be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient. Pharmaceutically acceptable carriers, in this regard, are intended to include any and all solvents, dispersion media, coatings, anti-bacterial and anti-fungal agents, isotonic and absorption delaying agents, and the like,

compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds (identified or designed according to the invention and/or known in the art) also can be incorporated into the compositions. The formulations may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy/microbiology. In general, some formulations are prepared by bringing the compound into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

A pharmaceutical composition of the invention should be formulated to be compatible with its intended route of administration. Examples of routes of administration include oral or parenteral, for example, intravenous, intradermal, inhalation, transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide.

Useful solutions for oral or parenteral administration can be prepared by any of the methods well known in the pharmaceutical art, described, for example, in Remington's Pharmaceutical Sciences, (Gennaro, A., ed.), Mack Pub., (1990). Formulations for parenteral administration can also include glycocholate for buccal administration, methoxysalicylate for rectal administration, or citric acid for vaginal administration. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Suppositories for rectal administration also can be prepared by mixing the drug with a non-irritating excipient such as cocoa butter, other glycerides, or other compositions which are solid at room temperature and liquid at body temperatures. Formulations also can include, for example, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, and hydrogenated naphthalenes. Formulations for direct administration can include glycerol and other compositions of high viscosity. Other potentially useful parenteral carriers for these drugs include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion

systems, and liposomes. Formulations for inhalation administration can contain as excipients, for example, lactose, or can be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or oily solutions for administration in the form of nasal drops, or as a gel to be applied intranasally. Retention enemas also can be used for rectal delivery.

Formulations of the present invention suitable for oral administration may be in the form of: discrete units such as capsules, gelatin capsules, sachets, tablets, troches, or lozenges, each containing a predetermined amount of the drug; a powder or granular composition; a solution or a suspension in an aqueous liquid or non-aqueous liquid; or an oil-in-water emulsion or a water-in-oil emulsion. The drug may also be administered in the form of a bolus, electuary or paste. A tablet may be made by compressing or molding the drug optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the drug in a free-flowing form such as a powder or granules, optionally mixed by a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered drug and suitable carrier moistened with an inert liquid diluent.

Oral compositions generally include an inert diluent or an edible carrier. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients. Oral compositions prepared using a fluid carrier for use as a mouthwash include the compound in the fluid carrier and are applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose; a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor ELTM (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). It should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms such as

bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filter sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation include vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Formulations suitable for intra-articular administration may be in the form of a sterile aqueous preparation of the drug that may be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems may also be used to present the drug for both intra-articular and ophthalmic administration.

Formulations suitable for topical administration, including eye treatment, include liquid or semi-liquid preparations such as liniments, lotions, gels, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops. Formulations for topical administration to the skin surface can be prepared by dispersing the drug with a dermatologically acceptable carrier such as a lotion, cream, ointment or soap. Particularly useful are carriers capable of forming a film or layer over the skin to localize application and inhibit removal. For topical administration to internal tissue surfaces, the agent can be dispersed in a liquid tissue adhesive or other substance known to enhance adsorption to a tissue surface. For example, hydroxypropylcellulose or fibrinogen/thrombin solutions can be used to advantage. Alternatively, tissue-coating solutions, such as pectin-containing formulations can be used.

For inhalation treatments, inhalation of powder (self-propelling or spray formulations) dispensed with a spray can, a nebulizer, or an atomizer can be used. Such formulations can be in the form of a fine powder for pulmonary administration from a powder inhalation device or self-propelling powder-dispensing formulations. In the case of self-propelling solution and spray formulations, the effect may be achieved either by choice of a valve having the desired spray characteristics (*i.e.,* being capable of producing a spray having the desired particle size) or by incorporating the active ingredient as a suspended powder in controlled particle size. For administration by inhalation, the compounds also can be delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.,* a gas such as carbon dioxide, or a nebulizer.

Systemic administration also can be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants generally are known in the art, and include, for example, for transmucosal administration, detergents and bile salts. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds typically are formulated into ointments, salves, gels, or creams as generally known in the art.

The active compounds may be prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. Liposomal suspensions can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

Oral or parenteral compositions can be formulated in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals. Furthermore,

administration can be by periodic injections of a bolus, or can be made more continuous by intravenous, intramuscular or intraperitoneal administration from an external reservoir (*e.g.*, an intravenous bag).

Where adhesion to a tissue surface is desired the composition can include the drug dispersed in a fibrinogen-thrombin composition or other bioadhesive. The compound then can be painted, sprayed or otherwise applied to the desired tissue surface. Alternatively, the drugs can be formulated for parenteral or oral administration to humans or other mammals, for example, in therapeutically effective amounts, *e.g.*, amounts that provide appropriate concentrations of the drug to target tissue for a time sufficient to induce the desired effect.

Where the active compound is to be used as part of a transplant procedure, it can be provided to the living tissue or organ to be transplanted prior to removal of tissue or organ from the donor. The compound can be provided to the donor host. Alternatively or, in addition, once removed from the donor, the organ or living tissue can be placed in a preservation solution containing the active compound. In all cases, the active compound can be administered directly to the desired tissue, as by injection to the tissue, or it can be provided systemically, either by oral or parenteral administration, using any of the methods and formulations described herein and/or known in the art. Where the drug comprises part of a tissue or organ preservation solution, any commercially available preservation solution can be used to advantage. For example, useful solutions known in the art include Collins solution, Wisconsin solution, Belzer solution, Eurocollins solution and lactated Ringer's solution.

Active compound as identified or designed by the methods described herein can be administered to individuals to treat disorders (prophylactically or therapeutically). In conjunction with such treatment, pharmacogenomics (*i.e.*, the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, a physician or clinician may consider applying knowledge obtained in relevant pharmacogenomics studies in determining whether to administer a drug as well as tailoring the dosage and/or therapeutic regimen of treatment with the drug.

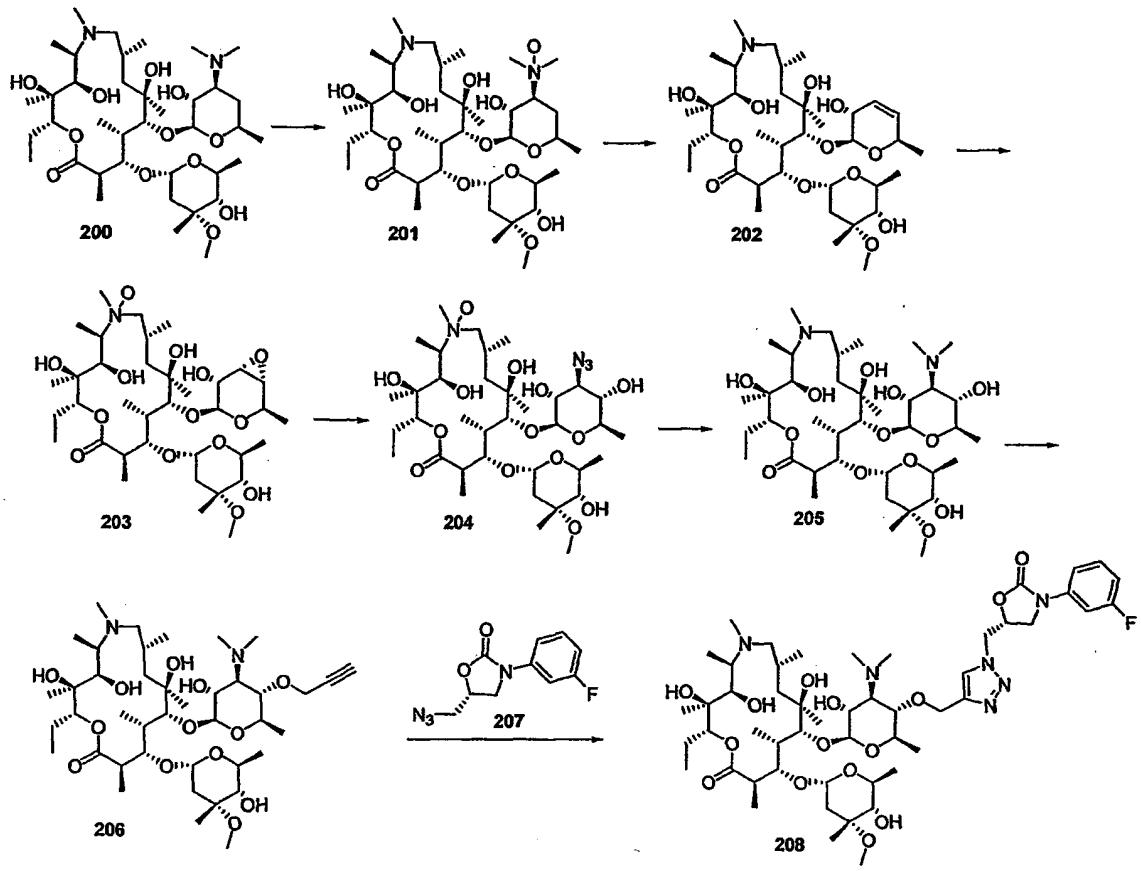
In therapeutic use for treating, or combating, bacterial infections in mammals, the compounds or pharmaceutical compositions thereof will be administered orally, parenterally and/or topically at a dosage to obtain and maintain a concentration, that is, an amount, or blood-

level or tissue level of active component in the animal undergoing treatment which will be anti-microbially effective. The term "effective amount" is understood to mean that the compound of the invention is present in or on the recipient in an amount sufficient to elicit biological activity, for example, anti-microbial activity, anti-fungal activity, anti-viral activity, anti-parasitic activity, and/or anti-proliferative activity. Generally, an effective amount of dosage of active component will be in the range of from about 0.1 to about 100, more preferably from about 1.0 to about 50 mg/kg of body weight/day. The amount administered will also likely depend on such variables as the type and extent of disease or indication to be treated, the overall health status of the particular patient, the relative biological efficacy of the compound delivered, the formulation of the drug, the presence and types of excipients in the formulation, and the route of administration. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or tissue level, or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, for example, two to four times per day.

6. Examples

Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Avance 300 or Avance 500 spectrometer, or in some cases a GE-Nicolet 300 spectrometer. Common reaction solvents were either high performance liquid chromatography (HPLC) grade or American Chemical Society (ACS) grade, and anhydrous as obtained from the manufacturer unless otherwise noted. "Chromatography" or "purified by silica gel" refers to flash column chromatography using silica gel (EM Merck, Silica Gel 60, 230-400 mesh) unless otherwise noted.

Example 1: Synthesis of Compound 208



Synthesis of Azithromycin-3'-*N*-oxide **201**

Azithromycin **200** (50 g, 66.8 mmol) was dissolved in enough warm acetone to make 150 mL of solution. This solution was allowed to cool to ambient temperature prior to addition of 40 ml of 30% w/w aqueous H_2O_2. Following a mild exotherm, the solution was allowed to cool to ambient temperature and stirred for 3.5 h. The reaction mixture was diluted to 2 L with CH_2Cl_2 and the resulting gelatinous mixture was stirred vigorously for 1h to afford a cloudy suspension. This suspension was washed with a 5:1 mixture of saturated aqueous $NaHCO_3$ and 10% w/v aqueous $Na_2S_2O_3$ (2 x 600 mL) and with brine (1 x 800 mL). The aqueous washes were combined and adjusted to pH 12 with 2N KOH and then further extracted with CH_2Cl_2 (3 x 300 mL). The combined organic extracts were dried over K_2CO_3, filtered, and concentrated *in vacuo*. As the volume of the extracts was reduced crystals began to form; when the total volume of the extracts had been reduced to 700 mL the solution was placed in a stoppered flask and stored at room temperature overnight. The solids were collected by vacuum filtration, rinsed with cold ether, and dried under vacuum to afford 34 g of white needle-like crystals. The filtrate

was treated as before to yield two additional crops of crystalline product **201** for a total yield of 51 g (66.7 mmol 99%). ^{1}HNMR (300 MHz, $CDCl_3$, partial): δ 5.06 (d, J = 4 Hz, 1H), 4.69 (d, J = 9 Hz, 1H), 4.53 (d, J = 7 Hz, 1H), 4.27 (d, J = 3 Hz, 1H), 4.11-4.02 (m, 1H), 3.75 (dd, J = 10, 7 Hz, 1H), 3.68 (s, 1H), 3.62 (d, J = 7 Hz, 1H), 3.46-3.39 (m, 1H), 3.37 (s, 3H), 3.20 (s, 6H), 3.04 (d, J = 9 Hz, 1H) 3.07-2.99 (m, 1H), 2.81-2.70 (m, 2H), 2.48 (d, J = 11 Hz, 1H), 2.42-2.25 (m, 2H), 2.15-1.84 (m, 2H), 1.78 (d, J = 15 Hz, 1H), 1.56 (dd, J = 15, 5 Hz, 1H), 1.54-1.40 (m, 1H), 1.29 (d, J = 6 Hz, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 1.18 (d, J = 7 Hz, 3H), 0.91 (t, J = 5 Hz, 3H), 0.86 (t, J = 7 Hz, 3H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 178.6, 102.5, 94.9, 78.4, 78.1, 77.8, 76.4, 74.3, 73.4, 72.9, 72.5, 66.9, 65.5, 59.1, 52.0, 49.7, 45.2, 41.8, 36.5, 34.9, 27.5, 26.7., 22.1, 21.6, 21.3, 18.5, 16.5, 15.0, 11.2, 9.0, 7.4. LCMS (ESI) *m/z* 765.6 $(M + H)^+$.

Synthesis of *3'* desdimethylamino-*4'*-dehydro-azithromycin **202**

A 300 mL pear-shaped recovery flask was charged with Azithromycin-*3'*-*N*-oxide **201** (35 g, 45.8 mmol) and placed on a rotary evaporator. The pressure was reduced to 0.5 torr and the flask was rotated slowly in an oil bath while the temperature was gradually increased to 175 °C. The mixture was held under vacuum at this temperature for 1.5 h then cooled to room temperature and flushed with argon. The resulting tan solid was dissolved in 800 mL of boiling acetonitrile. The solution was allowed to cool slowly to room temperature and then placed in a -20 °C freezer overnight. The solids were collected by vacuum filtration and washed with cold acetonitrile to afford 19.1 g of **202** as off-white crystals. The filtrate was concentrated and the residue treated as above to afford two additional crops of **202** product for a total yield of 27.7 g (39.4 mmol, 86%). ^{1}HNMR (300 MHz, $CDCl_3$, partial): δ 5.70-5.49 (m, 2H), 4.95 (d, J = 4 Hz, 1H), 4.64 (dd, J = 10, 2 Hz, 1H), 4.51 (d, J = 7 Hz, 1H), 4.40-4.29 (m, 1H), 4.25 (dd, J = 7, 2 Hz, 1H), 4.18-4.05 (m, 2H), 3.68 (d, J = 6 Hz, 1H), 3.65-3.59 (m, 2H), 3.28 (s, 3H), 3.03 (dd, J = 9, 11 Hz, 1H), 2.85 (p, J = 7 Hz, 1H), 2.74 (q, J = 7 Hz, 1H), 2.64 (bs, 1H), 2.55-2.40 (m, 3H), 2.35 (s, 3H), 2.30 (d, J = 15 Hz, 1H), 2.11-1.83 (m, 5H), 1.55 (dd, J = 10, 4 Hz, 1H), 1.55-1.45 (m, 1H), 1.37 (bs, 3H), 1.30 (d, J = 6 Hz, 1H), 1.24 (s, 3H), 1.23 (s, 3H), 1.21 (s, 3H), 1.10, (d, J = 8 Hz, 1H), 1.07 (s, 3H), 1.00 (d, J = 7 Hz, 3H), 0.91 (d, J = 7 Hz, 3H), 0.89 (t, J = 7 Hz, 3H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 176.3, 130.3, 124.5, 100.8, 94.0, 83.4, 77.7, 76.1, 75.9, 75.6, 73.2, 72.5, 71.7, 71.2, 68.3, 68.2, 67.0, 63.6, 60.1, 47.5, 43.1, 40.6, 38.6, 34.8, 33.1, 25.3, 24.9, 20.0, 19.7, 19.1, 16.2, 14.4, 13.9, 9.36, 7.9, 5.8. LCMS (ESI) *m/z* 704.5 $(M + H)^+$.

Synthesis of *3'* desdimethylamino-*4'*-dehydro-3',4'-epoxy-*9'N*-oxo-azithromycin **203**

To a methanol solution of **202** (25.0g, 35.5 mmol in 100 mL) was added *m*CPBA (20.4g, 39 mmol). The reaction mixture was stirred at room temperature for 14h at which time an additional 10g portion of *m*CPBA was added. The solution was stirred for an additional 4h, then diluted with 1200 mL CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ (2 x 500 mL) and brine (1 x 500 mL). The aqueous washes were back-extracted with CH_2Cl_2 (2 x 500 mL). The combined organic extracts were dried on K_2CO_3, filtered, and concentrated to give a white foam (30.7g) which was purified by silica gel chromatography (125mm x 6" column eluted with 7.5% 2N NH_3 in MeOH/ CH_2Cl_2) to afford compound **203** as a white solid (25.7 g, 35.0 mmol, 98%). ^{1}HNMR (300 MHz, $CDCl_3$): δ 5.10 (d, J = 4 Hz, 1H), 5.03 (dd, J = 8, 4 Hz, 1H), 4.41 (d, J = 7 Hz, 1H), 4.38 (d, J = 3 Hz, 1H), 4.22 (bs, 1H), 4.11 (d, J = 11 Hz, 1H), 4.04-3.92 (m, 1H), 3.52 (d, J = 8 Hz, 1H), 3.48-3.23 (m, 4H), 3.34 (s, 3H), 3.10 (d, J = 9 Hz, 1H), 2.99 (t, J = 10 Hz, 1H), 2.88 (bs, 3H), 2.72-2.60 (m, 2H), 2.58 (dd, J = 4, 7 Hz, 1H), 2.54-2.42 (m, 3H), 2.31 (d, J = 15 Hz, 1H), 2.29 (d, J = 10 Hz, 1H), 2.08-1.80 (m, 2H), 1.57 (d, J = 7 Hz, 1H), 1.54-1.38 (m, 3H), 1.37 (s, 3H), 1.28 (d, J = 6 Hz, 3H), 1.26 (d, J = 6 Hz, 3H), 1.23, (s, 3H), 1.18-1.10 (m, 6H), 1.04 (s, 3H), 0.96 (d, J = 6 Hz, 3H), 0.90 (t, J = 7 Hz, 3H). LCMS (ESI) *m/z* 779.6 $(M + H)^+$.

Synthesis of *3'*β-azido-*4'*α-hydroxy-*9'N*-oxo-3'-desdimethylamino-azithromycin **204**

Epoxide **203** (20.0g, 27.2 mmol) was dissolved in 88 mL of 10:1 DMSO-H_2O to which was added NaN_3 (17.7g, 270 mmol) and $Mg(ClO_4)\cdot 8H_2O$ (13.5g, 40.8 mmol). The mixture was stirred under argon at 85 °C for 16h then cooled to room temperature and poured into saturated aqueous $NaHCO_3$ (1L) and extracted with CH_2Cl_2 (5 x 500 mL). The combined organic extracts were dried over K_2CO_3, filtered, and concentrated to afford a white foam (29 g). This material was dissolved in hot CH_3CN (1.2L) and allowed to sit overnight at room temperature. The solids were filtered from the solution and rinsed with additional CH_3CN. The 8.7 g of crystalline solid thus obtained was confirmed by NMR and x-ray analysis to be pure *3'*α-hydroxy-*4'*β-azido-*9'N*-oxo-3'-desdimethylamino-azithromycin formed by addition of the azide at the 4' carbon of the epoxide. The mother liquors were concentrated and the residue again dissolved in boiling CH_3CN from which a second 3.0 g crop of the undesired isomer was obtained in pure form. The mother liquors, now enriched in the desired product **204**, were concentrated and the residue purified by silica gel chromatography (50 mm x 8" column eluted with 0-8% 2N NH_3 in MeOH/ CH_2Cl_2) to afford an additional 2.9 g of the earlier-eluting *4'*β-

azide along with the title compound **204** (6.5 g, 8.3 mmol, 31 %). ^{1}HNMR (300 MHz, $CDCl_3$): δ 5.01 (d, J = 4 Hz, 1H), 4.95 (dd, J = 8, 4 Hz, 1H), 4.40 (d, J = 7 Hz, 1H), 4.31 (d, J = 4 Hz, 1H), 4.15 (bs, 1H), 4.05 (d, J = 12 Hz, 1H), 3.97 (d, J = 7 Hz, 1H), 3.92 (dd, J = 9, 3 Hz, 1H), 3.66 (d, J = 7 Hz, 1H), 3.35 (bs, 1H), 3.35-3.31 (m, 1H), 3.25 (s, 3H), 3.23-3.15 (m, 1H), 3.05 (d, J = 4 Hz, 1H), 2.91 (t, J = 7 Hz, 1H), 2.81 (bs, 3H), 2.63 (bs, 1H), 2.56-2.36 (m, 4H), 2.33-2.26 (m, 1H), 2.23 (d, J = 15 Hz, 1H), 1.98-1.73 (m, 2H), 1.48 (d, J = 7 Hz, 1H), 1.45-1.27 (m, 4H), 1.25 (s, 3H), 1.23 (d, J = 7 Hz, 3H), 1.17, (d, J = 6 Hz, 1H), 1.13 (s, 3H), 1.07 (d, J = 7 Hz, 3H), 1.05 (d, J = 6 Hz, 3H), 0.99 (s, 3H), 0.89 (d, J = 7 Hz, 3H), 0.82 (t, J = 7 Hz, 3H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 177.7, 99.6, 94.5, 83.6, 78.2, 77.5, 76.7, 74.8, 74.5, 73.9, 72.8, 70.9, 69.4, 68.0, 65.0, 59.2, 55.9, 52.3, 49.2, 46.0, 43.8, 40.6, 34.8, 30.9, 27.0, 25.2, 22.8, 22.5, 21.7, 18.8, 17.8, 16.6, 14.9, 11.7, 9.9, 9.2. LCMS (ESI) *m/z* 736.6 $(M + H)^+$.

Synthesis of *4'*α-hydroxy-azithromycin **205**

A heavy-walled pressure tube was charged with an ethanol solution of **204** (1.73 g, 2.22 mmol in 20 mL) and 20% palladium on charcoal (0.14 g containing 50% H_2O). The reaction mixture was stirred under an H_2 atmosphere (15 psig) at room temperature for 14 h at which time 2 mL 37% aqueous CH_2O, 1 mL HCO_2H, and an additional 50 mg Pd on C were added. The hydrogen pressure was increased to 30 psig and stirring was continued for 24 h. At which time an additional 100 mg charge of Pd was added and the H_2 pressure was increased to 90 psig. After an additional 24 h at this pressure the reaction mixture was purged with argon, filtered, diluted with 100 mL toluene, and concentrated *in vacuo* to afford 1.9g of a colorless glass. The crude product was purified by silica gel chromatography (25 mm x 6" column eluted with 7% 2N NH_3 in MeOH/ CH_2Cl_2) to afford compound **205** as a white solid (0.78 g, 1.0 mmol, 45%). ^{1}HNMR (300 MHz, $CDCl_3$): δ 4.92 (d, J = 4 Hz, 1H), 4.61 (dd, J = 10, 2 Hz, 1H), 4.42 (d, J = 7 Hz, 1H), 4.18 (dd, J = 7, 2 Hz, 1H), 4.11-4.02 (m, 1H), 3.65-3.60 (m, 2H), 3.57 (dd, J = 10, 7 Hz, 1H), 3.33-3.23 (m, 1H), 3.28 (s, 3H), 3.05-2.95 (m, 2H), 2.86-2.62 (m, 3H), 2.52-2.38 (m, 2H), 2.47 (s, 6H), 2.35-2.27 (m, 2H), 2.32 (s, 3H), 2.10-2.62 (m, 5H), 1.55 (dd, J = 15, 5 Hz, 1H), 1.52-1.40 (m, 1H), 1.34 (s, 3H), 1.32 (d, J = 7 Hz, 1H), 1.28 (d, J = 6 Hz 3H), 1.22 (s, 3H), 1.19 (d, J = 6 Hz, 3H), 1.09 (d, J = 6 Hz, 3H), 1.04, (s, 3H), 0.97 (d, J = 7 Hz, 3H), 0.90 (d, J = 6 Hz, 3H), 0. 0.88 (t, J = 7 Hz, 3H). LCMS (ESI) *m/z* 765.5 $(M + H)^+$.

Synthesis of *4'*α-propargyloxy-azithromycin **206**

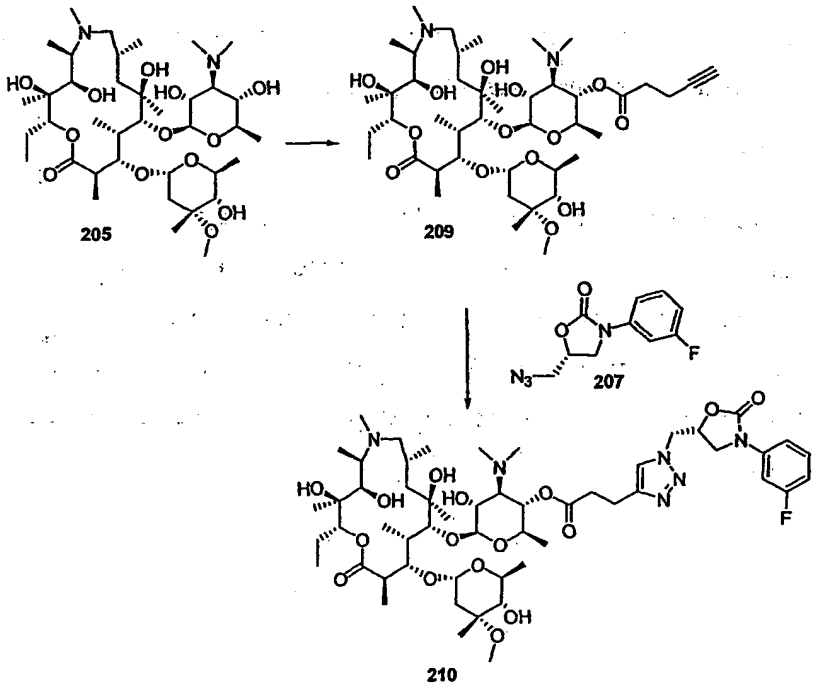
To a solution of 500 mg **205** (0.65 mmol) and 200 μL propargyl bromide (2.0 mmol) in CH_2Cl_2 (5 mL) was added 1 mL 50% w/w KOH(aq.) and 20 mg of $Bu_4N^+Br^-$. This mixture was

stirred vigorously at room temperature for 4h, then an additional charge of propargyl bromide (100 uL) and $Bu_4N^+Br^-$ (20 mg) was added. After stirring for 2 h more, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and water (50 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried on K_2CO_3, filtered, and concentrated to give 520 mg of an off-white foam. The crude product contains a mixture of starting material, mono-alkylated products (4''-propargyloxy-4'α-hydroxy-azithromycin and 2'-propargyloxy-4'α-hydroxy-azithromycin along with the desired product), and smaller amounts of bis-alkylated products. The desired product was recovered by preparative thin layer chromatography (plates developed with 7.5% 2N NH_3 in MeOH/ CH_2Cl_2) to afford compound **206** as a white solid (48 mg, 60 μmol, 9.1%). ^{1}HNMR (300 MHz, $CDCl_3$): δ 4.95 (d, J = 4 Hz, 1H), 4.60 (dd, J = 10, 2 Hz, 1H), 4.42 (d, J = 7 Hz, 1H), 4.38-4.33 (m, 2H), 4.29 (m, 1H), 4.23 (dd, J = 6, 2 Hz, 1H), 4.05-3.96 (m, 1H), 3.65-3.58 (m, 2H), 3.35-3.25 (m, 1H), 3.28 (s, 3H), 3.18 (t, J = 9 Hz, 1H), 2.99 (d, J = 9 Hz, 3H), 2.87-2.75 (m, 1H), 2.73-2.60 (m, 1H), 2.2.54-2.45 (m, 1H), 2.48 (t, J = 2 Hz, 1H), 2.35-2.20 (m, 2H), 2.32 (s, 3H), 2.10-1.80 (m, 4H), 1.75 (d, J = 15 Hz, 1H), 1.55 (dd, J = 15, 4 Hz, 1H), 1.55-1.40 (m, 1H) 1.34-1.15 (m, 18H), 1.08 (d, J = 6 Hz, 3H), 1.04, (s, 3H), 1.01 (d, J = 7 Hz, 3H), 0.92-0.81 (m, 6H). LCMS (ESI) *m/z* 803.5 $(M + H)^+$.

Synthesis of compound **208**

A 1 dram vial was charged with alkyne **206** (24 mg, 30 μmol), azide **207** (14 mg, 60 μmol) and THF (300 uL). The solution was degassed by alternately exposing to high vacuum and flushing with argon. CuI was added and the reaction stirred at room temperature for 3 h. The entire reaction mixture was placed on a preparative thin layer chromatography plate and eluted twice with 5% 2N NH_3 in MeOH/ CH_2Cl_2 to afford compound **208** as a white solid (18 mg, 17 μmol, 58 %). ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.72 (bs, 1H), 7.35-7.20 (m, 2H), 7.10-7.0 (m, 1H), 6.82-6.73 (td, J = 8, 2 Hz, 1H), 5.10-4.55 (m, 6H), 4.42 (d, J = 7 Hz, 1H), 4.2-3.7 (m, 5H), 3.65-3.50 (m, 2H), 3.31-3.15 (m, 2H), 3.25 (s, 3H), 2.95 (t, J = 10 Hz, 1H), 2.79-2.60 (m, 2H), 2.45 (bs, 6H), 2.28 (bs, 3H), 2.15-1.75 (m, 3H), 1.75 (d, J = 15 Hz, 1H), 1.49, (dd, J = 15, 4 Hz, 1H), 1.45-1.32 (m, 1H), 1.30-1.10 (m, 15H), 1.06 (d, J = 6 Hz,.3H), 0.9-0.78 (m, 6H). LCMS (ESI) *m/z* 520.4 $(M + 2H)^{2+}$, 1040.6 $(M + H)^+$.

Example 2: Synthesis of Compound 210



Synthesis of compound **209**

A solution of *4'*α-hydroxy-azithromycin **205** (50 mg, 0.066 mmol), 4-pentynoic acid (6.4 mg, 0.066 mmol) and dicyclohexyl carbodiimide (14.8 mg, 0.072 mmol) in CH_2Cl_2 (1.5 ml) was stirred at ambient temperature for 7h. The solution was filtered through a cotton plug, concentrated and purified by flash chromatography over silica gel (CH_2Cl_2: MeOH: NH_4OH = 20:1:0.05) to yield 35 mg of **209**. LCMS (ESI) *m/z* 423.4 $(M + 2H)^{2+}$, 845.6 $(M + H)^+$.

Synthesis of compound **210**

To a mixture of compound **209** (29 mg, 0.034 mmol), azide **207** (9.7 mg, 0.041) and CuI (3.27 mg, 0.017 mmol) was added THF (3 mL) and Hunig's base (0.050 mL). The solution was degassed with argon, and the resulting mixture was stirred under argon atmosphere at ambient temperature for 1h. Another portion of azide **207** (9.7 mg, 0.041 mmol) was added and the reaction mixture was stirred for additional 1h. The reaction mixture was poured into a saturated solution of NH_4Cl (25 mL) containing NH_4OH (3 mL) and stirred for 10 minutes. The resulting mixture was extracted with CH_2Cl_2 (3 x 50 mL), dried (anhydrous Na_2SO_4), concentrated and purified by flash chromatography over silica gel (CH_2Cl_2: MeOH: NH_4OH = 20:1:0.05) to yield 15 mg of compound **210**. LCMS (ESI) *m/z* 541.5 $(M + 2H)^{2+}$, 1081.8 $(M + H)^+$.

INCORPORATION BY REFERENCE

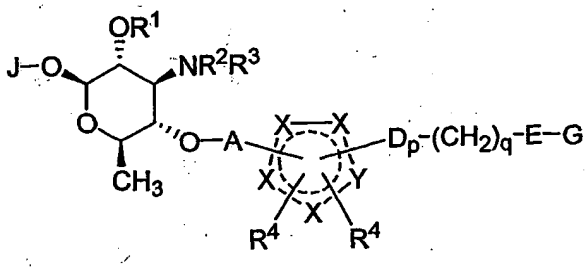
The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference herein for all purposes.

EQUIVALENTS

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

WHAT IS CLAIMED IS:

1. A compound having the formula:

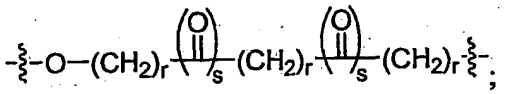


or a pharmaceutically acceptable salt, ester, or prodrug thereof,

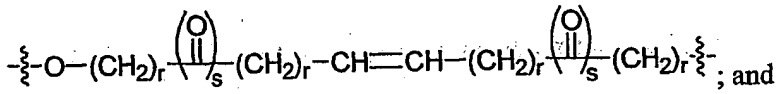
wherein:

-O-A is selected from the group consisting of:

a)

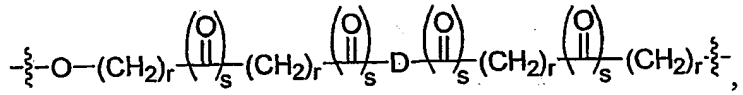


b)



; and

c)



wherein

r, at each occurrence, independently is 0, 1, 2 3, or 4, and

s, at each occurrence, independently is 0 or 1;

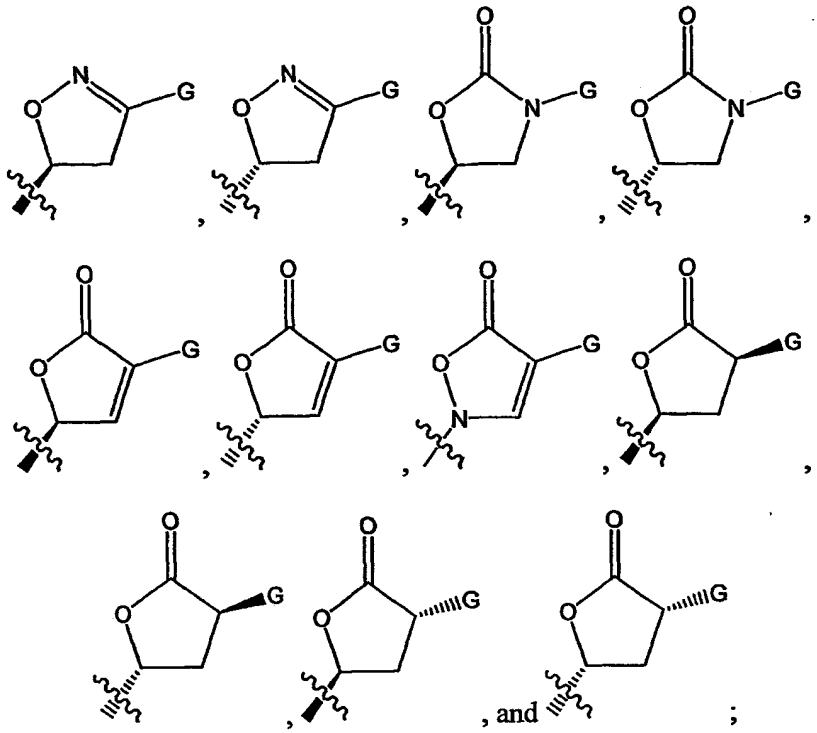
X, at each occurrence, independently is carbon, carbonyl, or nitrogen, provided at least one X is carbon;

Y is carbon, nitrogen, oxygen, or sulfur;

D is selected from the group consisting of:

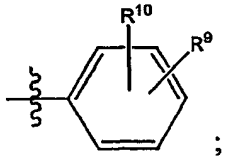
O, S, NR^5, C=O, C=S, C=NOR^5, SO, and SO_2;

E-G is selected from the group consisting of



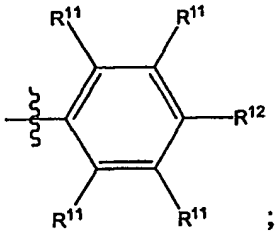
G is selected from the group consisting of:

a)



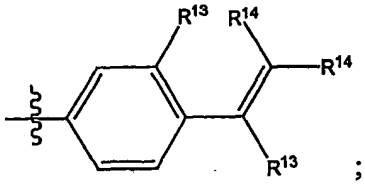
;

b)



;

c)



;

d) 3-14 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and optionally substituted with one or more R^4 groups;

e) C_{3-14} saturated, unsaturated, or aromatic carbocycle, optionally substituted with one or more R^4 groups;

f) C_{1-8} alkyl,

g) C_{2-8} alkenyl,

h) C_{2-8} alkynyl,

i) C_{1-8} alkoxy,

j) C_{1-8} alkylthio,

k) C_{1-8} acyl,

l) $S(O)_tR^5$; and

m) hydrogen,

wherein any of f) – k) optionally is substituted with

i) one or more R^4 groups;

ii) 3-14 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and optionally substituted with one or more R^4 groups; or

iii) C_{3-14} saturated, unsaturated, or aromatic carbocycle, optionally substituted with one or more R^4 groups;

J is selected from the group consisting of:

a) H, b) L_u-C_{1-6} alkyl, c) L_u-C_{2-6} alkenyl, d) L_u-C_{2-6} alkynyl, e) L_u-C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) L_u-(3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), and g) macrolide,

wherein

L is selected from the group consisting of -C(O)-, -C(O)O-, and -C(O)NR^5-,

u is 0 or 1, and

any of b) – f) optionally is substituted with one or more R^4 groups;

R^1, R^2, and R^3 are independently selected from the group consisting of:

a) H, b) L_u-C_{1-6} alkyl, c) L_u-C_{2-6} alkenyl, d) L_u-C_{2-6} alkynyl, e) L_u-C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) L_u-(3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), g) L_u-(saturated, unsaturated, or aromatic 10-membered bicyclic ring system optionally containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), and h) L_u-(saturated, unsaturated, or aromatic 13-membered tricyclic ring system optionally containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur),

wherein

L is selected from the group consisting of -C(O)-, -C(O)O-, and -C(O)NR^7-,

u is 0 or 1, and

any of b) – h) optionally is substituted with one or more R^4 groups;

alternatively, R^2, and R^3, taken together with the nitrogen atom to which they are bonded, form a 5-7 membered saturated, unsaturated, or aromatic heterocycle optionally containing one or more additional atoms selected from the group consisting of nitrogen, oxygen, and sulfur, and optionally substituted with one or more R^4 groups;

R^4, at each occurrence, independently is selected from the group consisting of:

a) F, b) Cl, c) Br, d) I, e) =O, f) =S, g) $=NR^5$, h) $=NOR^5$, i) $=NS(O)_tR^5$, j) $=N\text{-}NR^5R^5$, k) $-CF_3$, l) $-OR^5$, m) -CN, n) $-NO_2$, o) $-NR^5R^5$, p) $-NR^5OR^5$, q) $-C(O)R^5$, r) $-C(O)OR^5$, s) $-OC(O)R^5$, t) $-C(O)NR^5R^5$, u) $-NR^5C(O)R^5$, v) $-OC(O)NR^5R^5$, w) $-NR^5C(O)OR^5$, x) $-NR^5C(O)NR^5R^5$, y) $-C(S)R^5$, z) $-C(S)OR^5$, aa) $-OC(S)R^5$, bb) $-C(S)NR^5R^5$, cc) $-NR^5C(S)R^5$, dd) $-OC(S)NR^5R^5$, ee) $-NR^5C(S)OR^5$, ff) $-NR^5C(S)NR^5R^5$, gg) $-C(=NR^5)R^5$; hh) $-C(=NR^5)OR^5$, ii) $-OC(=NR^5)R^5$, jj) $-C(=NR^5)NR^5R^5$, kk) $-NR^5C(=NR^5)R^5$, ll) $-OC(=NR^5)NR^5R^5$, mm) $-NR^5C(=NR^5)OR^5$, nn) $-NR^5C(=NR^5)NR^5R^5$, oo) $-NR^5C(=NR^5)NR^5R^5$, pp) $-S(O)_tR^5$, qq) $-SO_2NR^5R^5$, rr) $-S(O)_tN=R^5$, and ss) R^5;

R^5, at each occurrence, independently is selected from the group consisting of:

a) H, b) L_u-C_{1-6} alkyl, c) L_u-C_{2-6} alkenyl, d) L_u-C_{2-6} alkynyl, e) L_u-C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) L_u-(3-14 membered saturated,

unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), g) L_u-(saturated, unsaturated, or aromatic 10-membered bicyclic ring system optionally containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), and h) L_u-(saturated, unsaturated, or aromatic 13-membered tricyclic ring system optionally containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur),

wherein

L is selected from the group consisting of -C(O)-, -C(O)O-, and $-C(O)NR^8$-,

u is 0 or 1, and

any of b) – h) optionally is substituted with one or more R^6 groups;

alternatively, two R^5 groups, taken together with the atom or atoms to which they are bonded, form i) a 5-7 membered saturated, unsaturated, or aromatic carbocycle, or ii) a 5-7 membered saturated, unsaturated, or aromatic heterocycle containing one or more atoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein i) - ii) optionally is substituted with one or more R^6 groups;

R^6, at each occurrence, independently is selected from the group consisting of:

a) F, b) Cl, c) Br, d) I, e) =O, f) =S, g) $=NR^7$, h) $=NOR^7$, i) $=NS(O)_tR^7$, j) $=N\text{-}NR^7R^7$, k) $-CF_3$, l) $-OR^7$, m) -CN, n) $-NO_2$, o) $-NR^7R^7$, p) $-NR^7OR^7$, q) $-C(O)R^7$, r) $-C(O)OR^7$, s) $-OC(O)R^7$, t) $-C(O)NR^7R^7$, u) $-NR^7C(O)R^7$, v) $-OC(O)NR^7R^7$, w) $-NR^7C(O)OR^7$, x) $-NR^7C(O)NR^7R^7$, y) $-C(S)R^7$, z) $-C(S)OR^7$, aa) $-OC(S)R^7$, bb) $-C(S)NR^7R^7$, cc) $-NR^7C(S)R^7$, dd) $-OC(S)NR^7R^7$, ee) $-NR^7C(S)OR^7$, ff) $-NR^7C(S)NR^7R^7$, gg) $-C(=NR^7)R^7$; hh) $-C(=NR^7)OR^7$, ii) $-OC(=NR^7)R^7$, jj) $-C(=NR^7)NR^7R^7$, kk) $-NR^7C(=NR^7)R^7$, ll) $-OC(=NR^7)NR^7R^7$, mm) $-NR^7C(=NR^7)OR^7$, nn) $-NR^7C(=NR^7)NR^7R^7$, oo) $-NR^7C(=NR^7)NR^7R^7$, pp) $-S(O)_tR^7$, qq) $-SO_2NR^7R^7$, rr) $-S(O)_tN=R^7$, and ss) R^7;

R^7, at each occurrence, independently is selected from the group consisting of:

a) H, b) L_u-$C_{1\text{-}6}$ alkyl, c) L_u-$C_{2\text{-}6}$ alkenyl, d) L_u-$C_{2\text{-}6}$ alkynyl, e) L_u-$C_{3\text{-}14}$ saturated, unsaturated, or aromatic carbocycle, f) L_u-(3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms

selected from the group consisting of nitrogen, oxygen, and sulfur), g) L_u-(saturated, unsaturated, or aromatic 10-membered bicyclic ring system optionally containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), and h) L_u-(saturated, unsaturated, or aromatic 13-membered tricyclic ring system optionally containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur),

wherein

L is selected from the group consisting of C(O), C(O)O, and $C(O)NR^7$,

u is 0 or 1, and

any of b) – h) optionally is substituted with one or more moieties selected from the group consisting of:

R^8, F, Cl, Br, I, $-CF_3$, $-OR^8$, $-SR^8$, -CN, $-NO_2$, $-NR^8R^8$, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-C(O)NR^8R^8$, $-NR^8C(O)R^8$, $-OC(O)NR^8R^8$, $-NR^8C(O)OR^8$, $-NR^8C(O)NR^8R^8$, $-C(S)R^8$, $-C(S)OR^8$, $-OC(S)R^8$, $-C(S)NR^8R^8$, $-NR^8C(S)R^8$, $-OC(S)NR^8R^8$, $-NR^8C(S)OR^8$, $-NR^8C(S)NR^8R^8$, $-NR^8C(NR^8)NR^8R^8$, $-SO_2NR^8R^8$, and $-S(O)_tR^8$;

alternatively, two R^7 groups, taken together with the atom or atoms to which they are bonded, form i) a 5-7 membered saturated, unsaturated, or aromatic carbocycle, or ii) a 5-7 membered saturated, unsaturated, or aromatic heterocycle containing one or more atoms selected from the group consisting of nitrogen, oxygen, and sulfur;

R^8, at each occurrence, independently is selected from the group consisting of:

a) H, b) L_u-C_{1-6} alkyl, c) L_u-C_{2-6} alkenyl, d) L_u-C_{2-6} alkynyl, e) L_u-C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) L_u-(3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), g) L_u-(saturated, unsaturated, or aromatic 10-membered bicyclic ring system optionally containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur), and h) L_u-(saturated, unsaturated, or aromatic 13-membered tricyclic ring system optionally containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur),

wherein

L is selected from the group consisting of -C(O)-, -C(O)O-, and -C(O)NH-, -C(O)N(C_{1-6} alkyl)-and

u is 0 or 1;

R^9 is R^4;

R^{10} is R^4;

alternatively, R^9 and R^{10}, taken together with the atoms to which they are bonded, form i) a 5-7 membered saturated, unsaturated, or aromatic carbocycle, or ii) a 5-7 membered saturated, unsaturated, or aromatic heterocycle containing one or more atoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein i) - ii) optionally is substituted with one or more R^4 groups;

R^{11} is R^4;

alternatively, two R^{11} groups, taken together with the atoms to which they are bonded, form i) a 5-7 membered saturated, unsaturated, or aromatic carbocycle, or ii) a 5-7 membered saturated, unsaturated, or aromatic heterocycle containing one or more atoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein i) - ii) optionally is substituted with one or more R^4 groups;

R^{12} is R^5;

alternatively, R^{12} and one R^{11} group, taken together with the atoms to which they are bonded, form i) a 5-7 membered saturated, unsaturated, or aromatic carbocycle, or ii) a 5-7 membered saturated, unsaturated, or aromatic heterocycle containing one or more atoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein i) - ii) optionally is substituted with one or more R^4 groups;

R^{13} is R^4;

R^{14} is R^4;

alternatively, any R^{13} and any R^{14}, taken together with the atoms to which they are bonded, form i) a 5-7 membered saturated, unsaturated, or aromatic carbocycle, or ii) a 5-7 membered saturated, unsaturated, or aromatic heterocycle containing one or more atoms selected from the group consisting of nitrogen, oxygen, and sulfur,

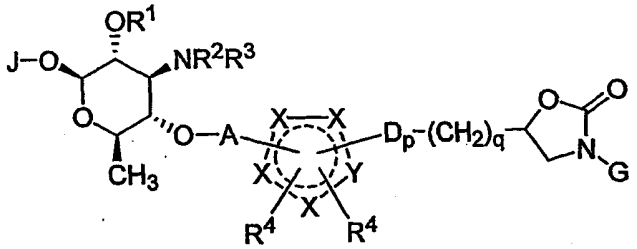
wherein i) - ii) optionally is substituted with one or more R^4 groups;

p is 0 or 1;

q is 0 or 1; and

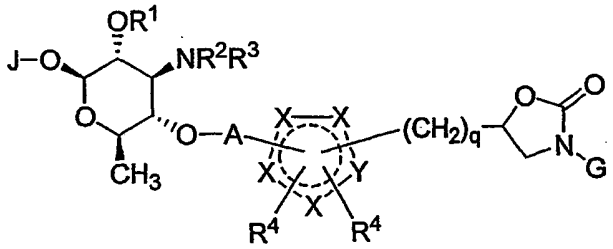
t, at each occurrence, independently is 0, 1, or 2.

2. The compound according to claim 1 having the formula:



wherein A, D, G, J, R^1, R^2, R^3, R^4, X, Y, p, and q are as defined in claim 1.

3. The compound according to claim 1 having the formula:



wherein

O-A is selected from the group consisting of:

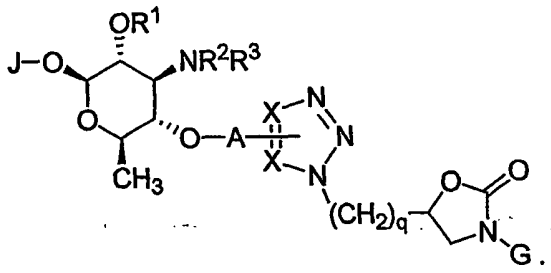
$O\text{-}(CH_2)_r$, O-C(O), and $O\text{-}C(O)\text{-}(CH_2)_r$;

r is 1, 2, 3, or 4;

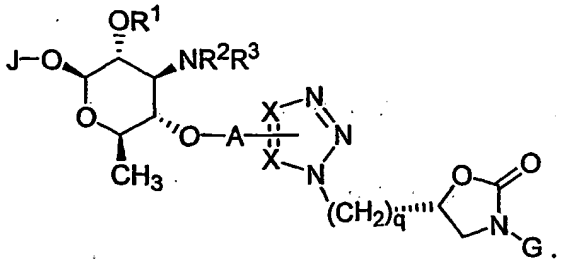
J is a macrolide; and

G, R^1, R^2, R^3, R^4, X, Y, and q are as defined in claim 1.

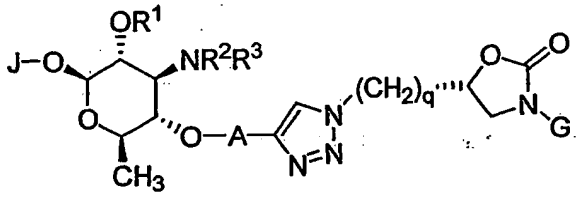
4. The compound according to claim 3 having the formula:



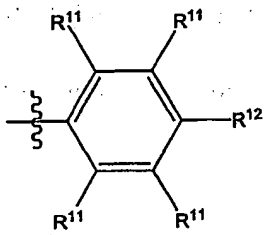
5. The compound according to claim 4 having the formula:



6. The compound according to claim 5 having the formula:

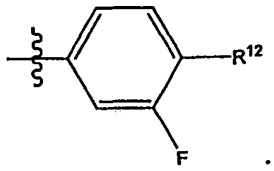


7. The compound according to claim 1, wherein G has the formula:



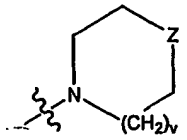
wherein R^{11} and R^{12} are as defined in claim 1.

8. The compound according to claim 7, wherein G has the formula:



9. The compound according to claim 8, wherein R^{12} is H.

10. The compound according to claim 8, wherein R^{12} has the formula:



wherein

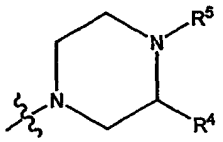
Z is selected from the group consisting of O, NR^5, and $S(O)_t$; and

v is 0, 1, 2, or 3.

11. The compound according to claim 10, wherein Z is O and v is 1.

12. The compound according to claim 7, wherein R^{12} is $-C(O)CH_3$.

13. The compound according to claim 7, wherein R^{12} has the formula:

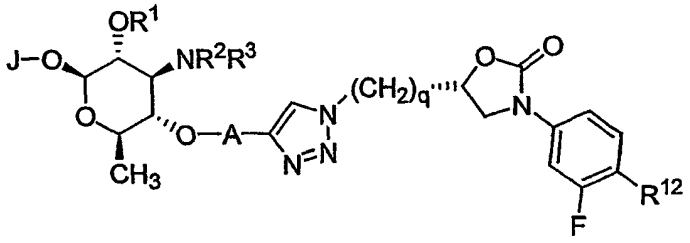


wherein R^4 and R^5 are as defined in claim 1.

14. The compound according to claim 13, wherein R^5 is $-C(O)-CH_2-OH$.

15. The compound according to claim 13, wherein R^4 is H.

16. The compound according to claim 1, having the formula:



wherein

O-A is selected from the group consisting of:

$O-(CH_2)_r$, O-C(O), and $O-C(O)-(CH_2)_r$;

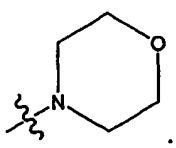
r is 1, 2, 3, or 4;

J is a macrolide; and

R^1, R^2, R^3, R^{12}, and q are as defined in claim 1.

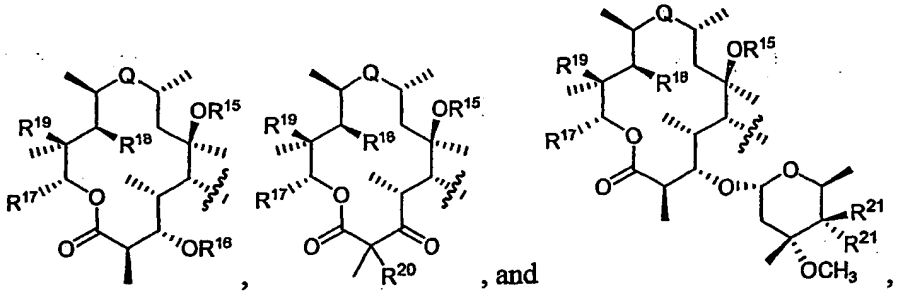
17. The compound according to claim 16, wherein R^{12} is H.

18. The compound according to claim 16, wherein R^{12} is



19. The compound according to claim 1, wherein J is a macrolide.

20. The compound according to claim 19, wherein the macrolide is selected from the group consisting of:



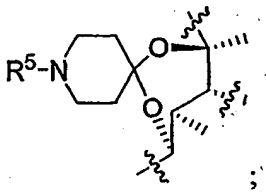
and pharmaceutically acceptable salts, esters and prodrugs thereof, wherein

Q is selected from the group consisting of:

$-NR^5CH_2-$, $-CH_2-NR^5-$, -C(O)-, -C(=NR^5)-, -C(=NOR^5)-, -C(=N-NR^5R^5)-, -CH(OR^5)-, and -CH(NR^5R^5)-;

R^{15} and R^{16} independently are selected from the group consisting of R^5 and a hydroxy protecting group;

alternatively R^{15} and R^{16}, taken together with the atoms to which they are bonded, form:



;

R^{17} is selected from the group consisting of:

a) C_{1-6} alkyl, b) C_{2-6} alkenyl, and c) C_{2-6} alkynyl;

wherein any of a) – c) optionally is substituted with one or more moieties selected from the group consisting of

i) $-OR^5$, ii) C_{3-14} saturated, unsaturated, or aromatic carbocycle, and iii) 3-14 membered saturated, unsaturated, or aromatic heterocycle containing one or more atoms selected from the group consisting of nitrogen, oxygen, and sulfur,

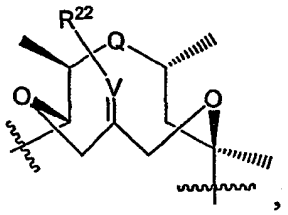
wherein any of ii) - iii) optionally is substituted with one or more R^4 groups;

R^{18} is selected from the group consisting of:

a) $-OR^{15}$, b) C_{1-6} alkyl , c) C_{2-6} alkenyl, d) C_{2-6} alkynyl, e) $-C(O)R^5$, and f) $-NR^5R^5$,

wherein any of b) - d) optionally is substituted with one or more R^4 groups;

alternatively, R^{15} and R^{18}, taken together with the atoms to which they are bonded, form:



wherein

V is CH or N, and

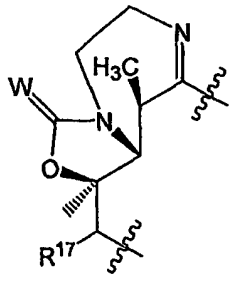
R^{22} is $-OR^5$, or R^5;

R^{19} is $-OR^{15}$;

alternatively, R^{18} and R^{19}, taken together with the atoms to which they are bonded, form a 5-membered ring by attachment to each other through a linker selected from the group consisting of:

$-OC(R^4)(R^4)O-$, $-OC(O)O-$, $-OC(O)NR^5-$, $-NR^5C(O)O-$, $-OC(O)NOR^5-$, $-N(OR^5)C(O)O-$, $-OC(O)N-NR^5R^5-$, $-N(NR^5R^5)C(O)O-$, $-OC(O)CHR^5-$, $-CHR^4C(O)O-$, $-OC(S)O-$, $-OC(S)NR^5-$, $-NR^5C(S)O-$, $-OC(S)NOR^5-$, $-N(OR^5)C(S)O-$, $-OC(S)N-NR^5R^5-$, $-N(NR^5R^5)C(S)O-$, $-OC(S)CHR^4-$, and $-CHR^4C(S)O-$;

alternatively, Q, R^{18}, and R^{19}, taken together with the atoms to which they are bonded, form:



wherein

W is O, NR^5, or NOR^5;

R^{20} is selected from the group consisting of:

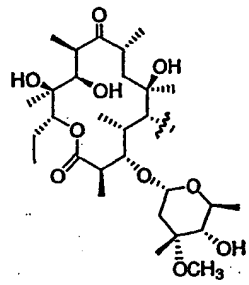
H, F, Cl, Br, and C_{1-6} alkyl;

R^{21}, at each occurrence, independently is selected from the group consisting of:

R^5, $-OR^{15}$, and $-NR^5R^5$;

alternatively, two R^{21} groups taken together are =O, =N-OR^5, or =N-NR^5R^5.

21. The compound according to claim 1, wherein J is selected from the group consisting of: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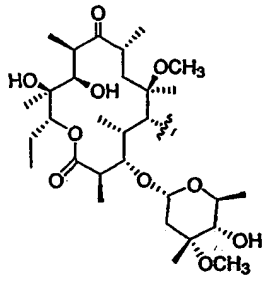
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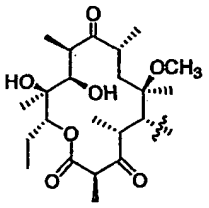
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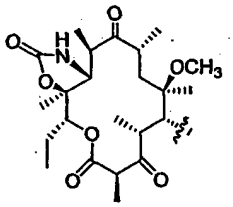
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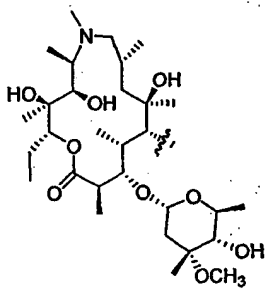
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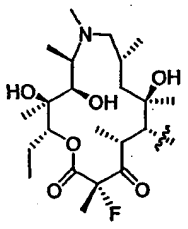
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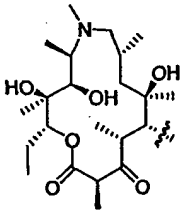
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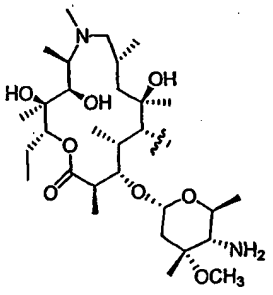
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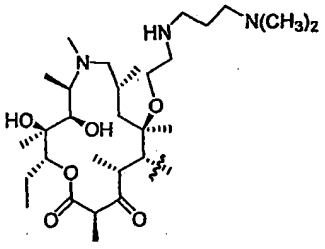
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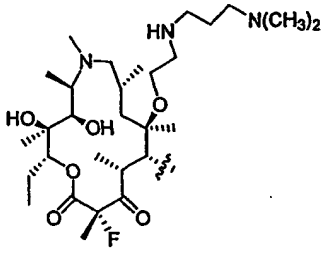
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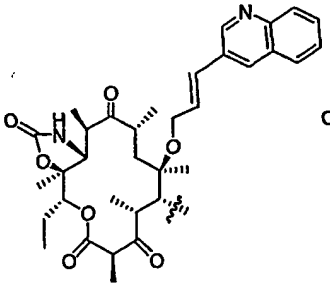
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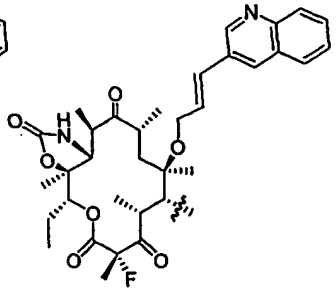
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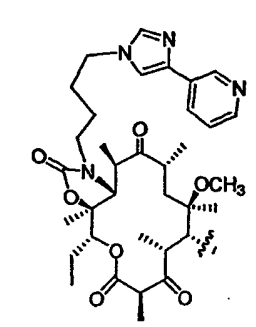
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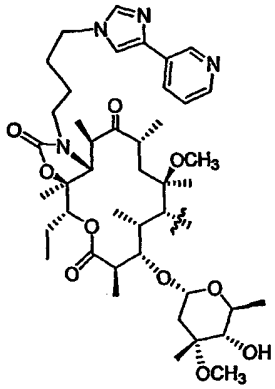
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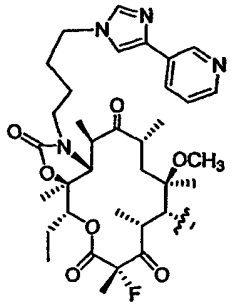
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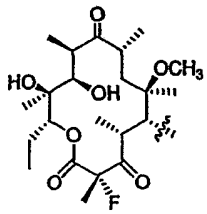
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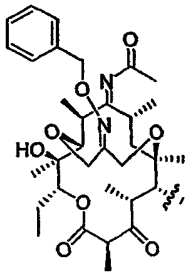
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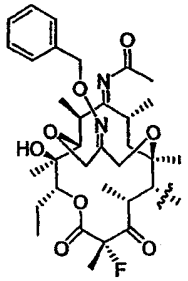
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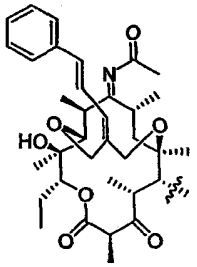
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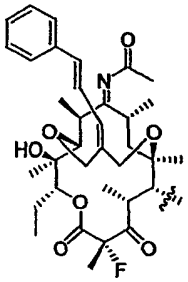
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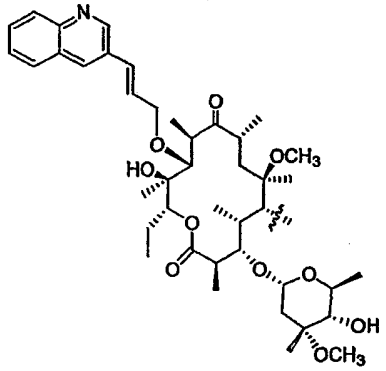
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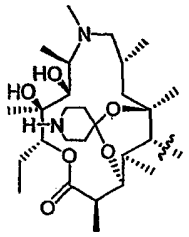
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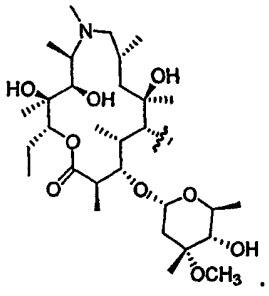
22. The compound according to claim 1, wherein J is: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23. The compound according to claim 1, wherein:

R^1 is H;

R^2 is methyl; and

R^3 is methyl.

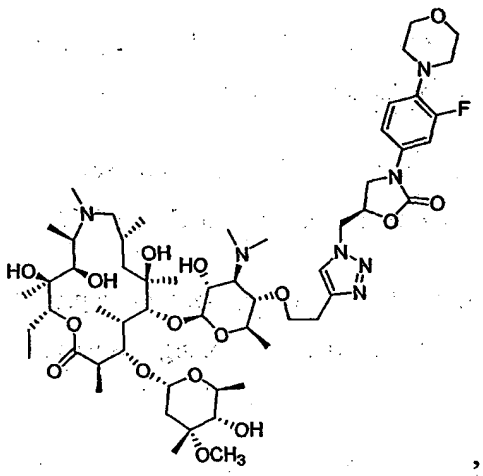
24. The compound according to claim 1, wherein:

R^1 is H;

R^2 is H; and

R^3 is methyl.

25. A compound having the structure selected from the group consisting of:



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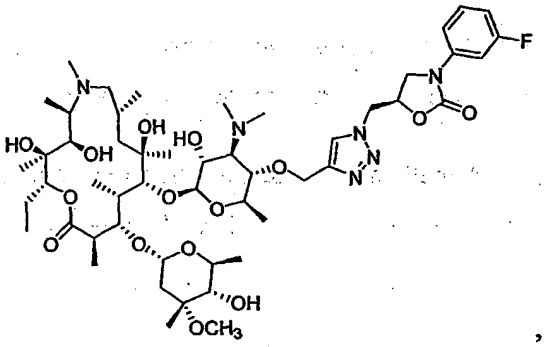

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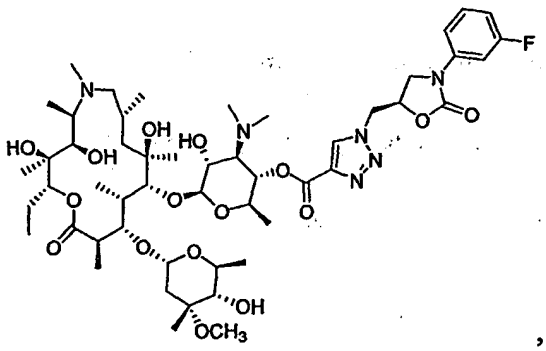

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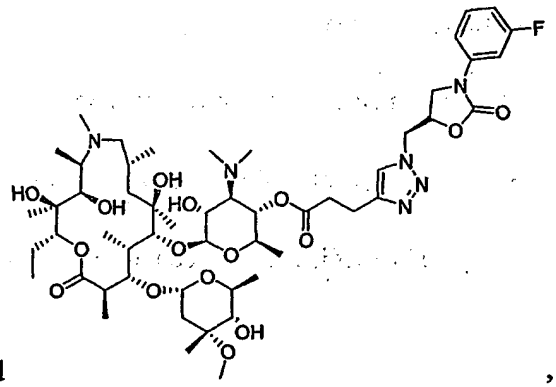

,

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

26. A pharmaceutical composition comprising a compound according to any one of claims 1-25 and a pharmaceutically acceptable carrier.

27. A method of treating a microbial infection in a mammal comprising administering to the mammal an effective amount of a compound according to any one of claims 1-25.

28. A method of treating a fungal infection in a mammal comprising administering to the mammal an effective amount of a compound according to any one of claims 1-25.

29. A method of treating a parasitic disease in a mammal comprising administering to the mammal an effective amount of a compound according to any one of claims 1-25.

30. A method of treating a proliferative disease in a mammal comprising administering to the mammal an effective amount of a compound according to any one of claims 1-25.

31. A method of treating a viral infection in a mammal comprising administering to the mammal an effective amount of a compound according to any one of claims 1-25.

32. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an effective amount of a compound according to any one of claims 1-25.

33. A method of treating a gastrointestinal motility disorder in a mammal comprising administering to the mammal an effective amount of a compound according to any one of claims 1-25.

34. The method according to any one of claims 27-33 wherein the compound is administered orally, parentally, or topically.

35. A method of synthesizing a compound according to any of claims 1-25.

36. A medical device containing a compound according to any one of claims 1-25.

37. The medical device according to claim 36, wherein the device is a stent.

INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/US2004/006892

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H17/00 C07H17/08 A61K31/7048 A61P31/04 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 693 791 A (TRUETT WILLIAM L) 2 December 1997 (1997-12-02) examples	1,27
A	EP 0 895 999 A (PFIZER PROD INC) 10 February 1999 (1999-02-10) abstract	1,27
A	WO 00/77016 A (MUTAK STJEPAN ; PLIVA D D (HR); LOPOTAR NEVENKA (HR); NARANDJA AMALIJA) 21 December 2000 (2000-12-21) abstract	1,27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 July 2004	06/08/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	de Nooy, A

INTERNATIONAL SEARCH REPORT

Information on patent family members

In ... onal Application No
PCT/US2004/006892

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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EP 0895999	A	10-02-1999	BR	9802851 A	29-08-2000
			CA	2244519 A1	06-02-1999
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			JP	3441377 B2	02-09-2003
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			EP	1189914 A1	27-03-2002
			WO	0077016 A1	21-12-2000
			HU	0201610 A2	28-10-2002
			JP	2003502338 T	21-01-2003
			NO	20016030 A	30-01-2002
			SK	17572001 A3	04-04-2002

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/006892

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons: .

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 27-34 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.